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AN IDEAL GIFT FOR SURGEONS, INTERNS OR RESIDENTS

ABDOMINAL OPERATIONS

By

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THE INTRACELLULAR ENVIRONMENT FOR INFECTIOUS AGENTS*

By ERNEST W. GOODPASTURE, M.D., *Nashville, Tenn.*

THE John Phillips Award was established in 1929 to honor the memory of a distinguished and beloved member of this College. Originally designed as a Fellowship, it was changed in 1934 to its present form which includes the John Phillips Award Lecture. It is very gratifying to me to be the recipient of the honor of addressing you today under the auspices of this Award. I am pleased to do so in order to make a sincere though small contribution to the memory of your former esteemed colleague, and to join the roster of medical scientists who have paid their tribute to him on similar occasions.

The Board of Regents by establishing the John Phillips Memorial Award expressed the interest of the College in scientific research as a fundamental factor in the development of Medicine. It has seemed to me proper therefore to indicate in this lecture my preoccupation for many years with problems of infection, especially those bearing upon pathogenesis and more specifically concerning host-parasite relations in infection caused by agents thus far uncultivable. These agents seem to require an intimate relation with individual cells of the host in order to survive, to multiply and incidentally to cause disease.

Many common infectious diseases are caused by familiar microörganisms like the pyogenic cocci and certain bacilli that can be easily cultivated in the test tube on dead media. These parasites can be identified by the pathologist in their respective lesions such as a boil, a cellulitis, a pneumonia or meningitis; and it is observed that they invade the host and multiply in various tissue fluids outside the cells. Because of their easy in vitro culture and their identification by means of the light microscope, this group of infectious agents has received a great deal of attention by bacteriologists, immunologists and pathologists, with the result that our general ideas of infection are

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From the Department of Pathology, Vanderbilt University, Nashville, Tenn.

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based largely upon knowledge gained from assiduous examination of them. Nevertheless these extracellular, cultivable microbes probably are considerably in the minority among parasitic agents in general, for there is a multitude of infectious diseases from which it has thus far been impossible to cultivate an etiological agent on lifeless media although the respective parasites in general can be seen, or have been identified in other ways, as occupants of living cells of the host.[1]

If the pathologist could magnify a patient, animal or plant, invaded by one of these uncultivable intracellular parasites, to the extent that he could observe the ultimate beginnings of infection, he would be able to witness a series of remarkable biological events associated with the state of obligate intracellular parasitism. First he would observe the attachment of a parasitic cell or unit to the surface of some active functioning cell of the host. The parasitic unit would be seen to penetrate the surface of the cell so as to gain admission into the protoplasm itself. Within this internal *milieu* some would multiply and remain confined to the cytoplasm, dispersed or in aggregations. In other cases, however, the original unit or early multiples of it would, by movements of cytoplasmic fluid, reach the nucleus, and in due course would penetrate its surface to become embedded in or suspended by the nucleoplasm. Here in some types of infection the parasitic particles would be seen to multiply within the nuclear sap and to induce changes there easily visible with the light microscope. If the parasites remain and multiply only in the cytoplasm, each assumes a pattern of growth with respect to the structure of the cell that may be quite characteristic and perhaps indicative of the presence of local conditions in protoplasm exclusively adaptable to its needs.

The multiplication of parasitic units in cytoplasm or nucleus would be accompanied by a strange variety of imbalances in the normal energies of the cell, expressing themselves in observable gross results, such as mitosis, structural abnormalities or necrosis. The multiplication of these effects and their chains of sequelae would culminate in the symptoms and signs of one or another of the specific infections.

With knowledge at hand, and in the expansive era in which we find ourselves, it is not difficult to imagine such an enlarged picture of what has now become accepted as representative of the gross aspects of cell-parasite relationship in certain infectious diseases. But the light microscope fails us when we would seek to discern the intimacies and intricacies of interactions that transpire within the infected cell. If there were no hope of other instrumentalities and methods of following these events the observations which I wish to bring to your notice in this lecture would have of themselves little of interest.

It is my purpose to point out in instances of intracellular parasitism some observable relations of host-cell and invader that might be interpreted to indicate an organization of activity within infected cells which influences the

parasite profoundly. With the presence and promise of methods applicable to explorations of the now largely recondite structure and function of cells in their molecular aspects, and those of parasites of varying complexity, there is justifiable hope that the cell-parasite relationship will constitute a fertile field for the cytologist of the future equipped for such an adventure.

For several years in my laboratory we were concerned with evidence that parasites including virus particles actually do enter the protoplasm of cells and multiply there, because during earlier investigations of virus infections at least it was largely a matter of conjecture whether or not virus multiplied outside, on the surface of or only in the interior of the cells affected. The specific intracellular inclusions of certain virus diseases were thought by some observers to be mere products of degeneration. The problem was a difficult one because virus particles as such are not identifiable with certainty in the intact cell. In the case of protozoal, bacterial and rickettsial infections one could proceed with more confidence, because these parasites could be seen and identified by their morphological features.

To explore the relationship of virus to infected cells Dr. Eugene Woodruff and I concentrated on the disease fowl-pox, and succeeded in demonstrating that virus is not only present in the infected cell but constitutes a large component of the specific cellular inclusion, the Bollinger body.[2]

In fowl-pox the virus affects particularly epithelial cells of unfeathered parts of chicken skin. The initial lesion might be located in epithelium of the oral mucosa or in the crop. From such a focus virus enters the blood stream and localizes secondarily in unfeathered skin areas, such as the comb, wattles, eyelids and follicles if the feathers be plucked. The epithelial cells multiply by mitosis and individually enlarge to form a wart-like nodule or pock. The infection starts in the basal layer of epithelial cells and eventually it seems that every cell in the lesion gives evidence of involvement. Specifically each cell comes to contain a large round, oval or slightly lobulated refractive body or mass situated in the cytoplasm. The volume of the cell is increased apparently by an excess of water, and in fixed preparations the cytoplasm is pale and delicately reticulated.

When the infected tissue is fragmented and placed in an alkaline solution of trypsin the cells disintegrate and the compact inclusions are liberated. The latter are so substantial and of such consistency that they were easily manipulated. After repeated washings no virus was demonstrated in the fluid bathing them, yet when they were picked up individually in a capillary pipette and inserted into a follicle from which the feather had been plucked, that follicle developed the typical lesion of fowl-pox. Likewise a follicle could be infected by inserting into it a fragment of a single inclusion. Thus it was demonstrated that the specific intracellular inclusion of fowl-pox is individually and fractionally infective. Each specific inclusion or Bollinger body is composed of thousands of coccoid structures of uniform size just visible with the light microscope. These particles, the so-called elementary

bodies, are embedded in a lipoprotein matrix that gives form and consistency to the inclusion. The elementary bodies are now considered to represent virus units.

These experiments I believe offer the clearest demonstration of the presence of virus within infected cells and in association with a specific inclusion, although there is much other evidence of various sorts that strengthens the view that all known viruses enter cells and multiply only in a protoplasmic medium. It is less difficult to assure oneself that certain protozoa, bacteria and rickettsia invade cells and multiply in them, because these parasites are larger, more characteristic in their morphology and can be colored by suitable dyes which disclose distinctive characters. Consequently the now generally accepted view that many kinds of parasites penetrate and multiply exclusively in living cells of the host has a very substantial justification from observation and experiment.

Accepting the evidence then that in many specific infections individual parasites or infective agents in some fashion, usually obscure, find their way to the surface of specific living cells, penetrate them through the interplay of surface tensions, and multiply in the protoplasmic medium, the pathologist is confronted with the ultimate problem of cytology toward which much biological investigation is now converging, namely, the structure and function of the living cell—in this case the structure and function of the living cell as a culture medium for parasites.

Infectious agents are delicate indicators of differences in protoplasmic media and inasmuch as they can gain admittance, the one or another of them, to the interior environment of probably every type of cell in animal and plant bodies, I suspect that they will prove to be most useful tools with which to explore experimentally intracellular organization and activities. It is my chief purpose to point out just a few significant though gross indications that infectious agents are extremely sensitive to conditions in the protoplasmic environment. It appears from these indications that protoplasm may not be homogeneous in structure or uniform in activity with respect to its adaptability to requirements of the parasite but may be possessed of an organization that is reflected by the behavior of the invading agent, and further that the parasitic agent can alter profoundly and in different ways the intracellular medium which it at first utilizes for its own reproduction.

Not only are obligate intracellular parasites naturally host-adapted but it is well known that they are highly specific with respect to their ability to induce lesions in the different types of cell of a susceptible host. Sometimes with a particular virus this cell specificity is amazing. One of the most striking examples in our experience is the behavior of the virus of canine oral warts. This is not an uncommon disease of dogs and manifests itself by papillomatous growths upon the oral mucosa especially of the lips. These growths sometimes attain a considerable size that is, a few centimeters in diameter. The virus is easily filterable, and upon inoculation by injection

into or scarification of the oral mucosa it reveals its effects after about 30 days by the presence of epithelial plaques which grow rapidly. All of our efforts to infect other epithelia of the dog, including that of perioral skin, conjunctiva, prepuce and vagina, entirely failed.[3] This lack of ability of the virus to affect other than oral epithelium might be due to an inability to penetrate other cells or to failure of their protoplasm to provide suitable conditions for its multiplication. It would seem that the latter were more likely, for some viruses at least can become modified by continued passage in unusual environments so that they multiply abundantly in cells to which the original strain was unaccustomed. We have observed this both with strains of vaccinia and herpes simplex viruses.

It is of especial interest to observe that after an obligate intracellular parasite enters the cytoplasm of a cell able to support its growth, conditions existing therein determine whether or not it will be best accommodated by one of the two chief structural components namely, the cytoplasm or the nucleus. It is not known whether every infectious agent of this kind that gains access to the cytoplasm likewise penetrates the nucleus, but if so only certain ones find in that organ advantageous conditions for multiplication. It is possible that some infectious agents can only be reproduced within nucleoplasm and simply pass through the cytoplasm without being affected by it. In any case those that are known to multiply in the nucleus appear to penetrate its surface in much the same manner as they do the cytoplasmic surfaces. The intranuclear environment has long been known to afford conditions for parasitic growth in some of the lower forms of life, such as the paramecia. Among the infective diseases of the protozoa, one that has received careful study is that induced by several representatives of a particular genus of microörganisms discovered, according to Metchnikoff, by Johannes Muller in 1856 and investigated by Hafkine.[4] Hafkine found that paramecia are occasionally infected by needle-shaped or spirillar parasites which penetrate, sometimes into the macronucleus, sometimes into the micronucleus, reproducing prolifically only in these structures and giving rise to a marked hypertrophy of them. In spite of this invasion the paramecium may continue to exist and carry on its reproductive processes.

Among infections of higher animals many examples could be cited where evidence indicates a similar penetration of parasites into the nucleus and proliferation there. Wolbach[5] observed rickettsia of Rocky Mountain Spotted Fever in nuclei of certain epithelial cells of ticks, and Pinkerton and Hass[6] reproduced a similar picture by means of tissue cultures infected with this microörganism. Virus infections afford many instances of nuclear involvement characterized by the presence of specific inclusions which presumably indicate the local presence of the infectious agent. Among these diseases are herpes simplex, zoster and chicken-pox. There is little corresponding evidence that virus multiplies in both cytoplasm and nucleus, excepting the coincidence of inclusions in nucleus and cytoplasm in cells from

canine distemper and the salivary gland disease.[7, 8] That special favorable conditions exist for virus multiplication either within the nucleus or in the cytoplasm, possibly exclusively in particular instances, is indicated by the fact that a single cell can be infected by two viruses simultaneously, the one, for example herpes simplex, inducing characteristic changes in the nucleus, the other, be it fowl-pox, vaccinia or rabies, bringing about its specific inclusion in the cytoplasm.[9]

Not only may parasites find their most fertile soil in either nucleus or cytoplasm but of particular interest is the topographical relationship of certain of these agents to the latter medium in which they orient themselves in such a way as to indicate a structural and functional organization that offers some parasites a preferential environment for multiplication. I should like therefore to direct your attention to several instances of specific infections in which the intracytoplasmic parasite characteristically occupies a particular locus in the cytoplasm. Examples may be drawn from protozoal, bacterial, rickettsial and viral infections and they will be considered in this order.

One of the most striking examples of "selective" localization of a protozoan parasite in the cytoplasm of infected cells was described by Tyzzer [10] in his study of coccidiosis in gallinaceous birds. So constant were the positions assumed by different species of coccidia within the same type of epithelial cells of the intestine of chickens that their respective locations were most helpful in distinguishing them. Following is Tyzzer's description:

> By a comparative review of the relation established by parasite and host-cell, various depths of penetration and a variety of reactions became apparent. In Cryptosporidium we have a coccidium which penetrates the cuticular layer but never enters the cytoplasm of the epithelial cell. As it increases in size it bulges out from the surface of the epithelium but nevertheless remains fixed to the cuticular layer. *Eimeria acervulina* penetrates the cytoplasm but the small growing forms are very superficially situated. The schizonts require more space but lie just beneath the surface. . . . *Eimeria mitis* penetrates deeply so that it commonly starts its development in the region of the cell's nucleus, and often below it. . . . Such distinctive host-cell-reactions are of considerable assistance in the differentiation of species.

Similar though less striking instances of intracellular localization can be found in certain bacterial infections. Recent studies of Buddingh and Womack [11] have shown that the developing chick embryo can be readily infected by the Brucella group of microörganisms. These bacteria show an especial predilection for vascular endothelium. They penetrate these cells and proliferate abundantly in their cytoplasm. They can likewise penetrate and grow within the cytoplasm of certain epithelial cells including those of the hepatic parenchyma. It is in the liver indeed that a rather striking contrast can be observed between the pattern of growth within the Kupffer cells and that within parenchymal epithelium. The difference is sufficiently distinct to permit one easily to distinguish the two types of infected cells although each is filled with parasites. In the infected liver cell the micro-

organisms appear to be uniformly distributed throughout the cytoplasm increasing its bulk considerably. In the cytoplasm of a Kupffer cell they are distinctly compartmentalized as if there were numerous colonies separated by cytoplasmic partitions. This disposition of the multiplying parasites might be attributed to a segregating effect of cytoplasmic activity or to a possible compression of protoplasmic fibers or to a gelation of the medium resulting from bacterial products. No such segregation is to be observed in infected hepatic cells or in those of the chorionic epithelium. In other similar experiments with *Pasteurella tularense,* infected epithelium of chorion and liver showed no evidence of compartmentalization.

In leprosy we have an example of an infectious disease in which a bacillary parasite penetrates certain cells of the host and multiplies apparently exclusively in the cytoplasmic medium. Although some types of epithelium may be penetrated and can afford suitable conditions for growth, it is the large mononuclear mesodermal "lepra cell" that is characteristically involved and accounts for the peculiar histologic features of leprosy. The intracytoplasmic environment of these cells is the preferential and presumably the essential soil for the maintenance of the parasite and consequently of the disease.

It is characteristic of the "lepra cell" that there are multiple foci or colonies of Hansen's bacillus in single cells including the giant cells that frequently form in a lesion. These compact and compartmentalized colonies, separated by cytoplasmic partitions, form the characteristic "globi," familiar to the student of leprosy. There is some indication that they form about the surfaces of droplets of fat which accumulate in the "lepra cell," reminiscent of the capsule of elementary bodies of fowl-pox in early stages of infection of epithelial cells in which lipoid droplets appear as the first microscopic evidence of infection.

Although the parasite of leprosy enters and grows on occasions within epithelium of the skin and sweat glands, compartmentalization and the formation of multiple "globi" do not occur in these cells.

Although obligate intracellular parasitism of the bacillus of leprosy can be reasonably assumed, there is better evidence that rickettsia multiply only in living cells. In his studies of the lesions of Rocky Mountain spotted fever in mammals and in the tick, Wolbach first described the localization of the rickettsia within cells of the former generally in the cytoplasm of endothelium and in smooth muscles of arterioles; but in infected ticks, they were also situated within nuclei of the epithelial cells of the Malpighian tubules, rectal sac, intestine and salivary glands. Intracellular localization of these parasites was especially studied by Pinkerton and Hass by means of tissue cultures of membranous exudate from the scrotal sac of infected guinea pigs. These authors described the outstanding feature of the picture to be the predilection of the rickettsia for the nuclei of cells. In several preparations, the majority of infected cells showed only nuclear involvement. The

majority of cells in which the cytoplasm was infected contained less than 50 microörganisms, and in no instance did the entire cytoplasmic volume become occupied by closely packed microörganisms. This was in striking contrast with similar cells infected by the rickettsia of louse borne typhus. In typhus infection the nucleus of involved cells never contained parasites but the cytoplasm became distended with great masses of them. It is of interest that infection of the nucleus with Rocky Mountain spotted fever parasites was characterized by a clustering of the microörganisms into more or less compact masses distributed through the nucleoplasm. The reason for the clustering of parasites in nuclei and their diffuse distribution in cytoplasm was not apparent. One may judge from these experiments that the cytoplasm of the scrotal cells is not a good medium for growth of the parasites and that not infrequently a microörganism enters it only to traverse its substance, reach the nucleus, penetrate it and multiply therein abundantly. In contrast these investigators found that typhus rickettsia occasionally form separate groups in the cytoplasm of the cells in which they grow. The partitions between the groups are often indefinite because the cytoplasm becomes filled to the point of bursting.

Recently I had the opportunity to study epithelial cells of the mucosa of the yolk sac of chick embryos which were infected as a result of injecting pure cultures of a variety of pathogenic microörganisms into the yolk. Included in the group studied were yolk sacs infected with louse-borne, and others infected with flea-borne rickettsias of typhus fever. The contrasting intracellular localization of the parasites was striking. In neither infection were nuclei penetrated as in Rocky Mountain spotted fever, but heavy intracytoplasmic growth occurred. In the case of *R. prowazeki* epithelial cells became filled and distended by parasites which in different cells presented two morphological appearances. In the great majority the cytoplasm became filled with minute coccoid or short bacillary forms. More rarely other cells contained exclusively long filamentous forms apparently interwoven in a loose fashion. These two forms of this parasite have been noted by Wolbach and by Pinkerton and Hass, but no satisfactory explanation of the difference is at hand.

Epithelium of the yolk sac infected with *R. mooseri* presented a quite different and a significant picture. In each infected cell the growing mass of flea-borne rickettsia was located only in the basal pole between the nucleus and the basement membrane. There was no distention of cells and no apparent involvement of the cytoplasm distal to the nucleus. It seems quite clear from these preparations that epithelial cells of the chick yolk-sac afford for this rickettsia localized, favorable conditions within the cytoplasm restricted to the basal pole and most favorable adjacent to the nucleus. So far as I know such an intracellular disposition of this parasite has not hitherto been described.

Among virus infections only those that afford evidence of location and growth within cells, such as by the formation of inclusions which can be

interpreted to be partly composed of elementary virus particles, permit one to speculate upon possible intracellular organization that might provide specially favorable or unfavorable environments for their multiplication. It can be reasonably conjectured from numerous examples that some viruses enter and multiply within the nucleus, perhaps exclusively, while others remain confined to the cytoplasm. There is no clear indication at present that different parts of the nucleus provide more or less favorable conditions for virus growth although it appears that nuclear activity and structure may be affected differently by different infectious agents that presumably multiply within it.

A variety of morphological appearances in the cytoplasm of infected epithelial cells can be illustrated by examples from the pox group of virus lesions. These infections have the advantage too that their etiological agents are quite comparable with each other and are large enough to be identified in suitably stained preparations, so that their participation in the composition of the respective cytoplasmic inclusions is no longer reasonably in doubt.

In fowl-pox the first indication of infection of an epithelial cell is the occurrence of one or more small globules of fat apparently indiscriminately distributed within the cytoplasm. They enlarge and one can then demonstrate about them an encapsulation of acidophilic material. This material increases proportionately as the inclusion enlarges. The bodies scattered through the cytoplasm move about in such a way as to join each other eventually to form by fusion a single large spherical, oval or irregularly elliptical mass which constitutes the "mature" Bollinger body. This consists of thousands of elementary bodies embedded in a lipo-protein matrix. There is no indication that one area of the cytoplasm is more adaptable to their formation than another. Nucleoli may become enlarged and nucleolar particles may be extruded into the cytoplasm.

Infection of human cutaneous epithelium with virus of molluscum contagiosum likewise manifests itself by cytoplasmic changes but of a different kind.[12] In early stages of infection conspicuous nucleolar disturbances are observed although the virus is confined to the cytoplasm. The nucleoli enlarge and conspicuous particles of nucleolar material, often surrounded by a sort of misty halo, appear in the cytoplasm. Early evidences of cytoplasmic involvement are observed in the central portion of the cytoplasm. Here there seems to be a sort of condensation about which a series of clear vacuoles are seen in fixed preparations. These vacuolated areas probably contained a clear fluid in which no fat is stainable. About the periphery of the vacuoles dense confluent zones appear in the cytoplasm and in this denser material lie the elementary molluscum bodies, indistinguishable in stained smear preparations from those of fowl-pox, small-pox and vaccinia. The dense and basophilic material increases in amount until it finally quite fills the cell and distends it, the nucleus being forced to the periphery. At this final stage no vacuoles are to be seen, but the architecture of the cytoplasm with its abundance of newly formed elements is quite characteristic in that it is definitely

compartmentalized by thin partitions which outline the separate areas filled with elementary bodies. The elementary bodies are held together by a sticky substrate which prevents manipulation of the gross inclusion after digesting the cytoplasmic surfaces and partitions by means of trypsin. In the development of infection with the virus of molluscum contagiosum then, there does not appear to be an indiscriminate localization in the cytoplasm but rather a preferential one in the center of its mass.

With the viruses of small-pox and vaccinia the case is different for both of them develop their respective cytoplasmic inclusions (Guarnieri bodies) in close relation to the nucleus of the infected cell. The surface of the nucleus on one or two sides is frequently indented by the inclusions. In the case of vaccinia, especially in infections of the chick embryo, large pyramidal inclusions are seen with their bases closely adjacent to the nucleus. One can infer from such appearances that a perinuclear environment is especially adaptable to multiplication of these immunologically closely related parasites.

These examples of intracellular parasitism should be sufficient to illustrate the variable interactions and relationships that transpire during the adaptations of the substances and energies of the parasite on the one hand and those of the host-cell on the other. They likewise indicate the presence of peculiar conditions in the cell supporting multiplication of a parasite which predispose to a localization and proliferation of the infectious agent either in the nucleus, or in the cytoplasm, rarely in both. Furthermore morphological changes are presented that can be adduced as evidence of the existence of a structural and functional organization of the cytoplasmic medium that affords a topographically preferential orientation to the multiplication of a particular parasite. In one instance it might be the immediate perinuclear environment as in vaccinia and endemic typhus, in another the base of the cell or its antipode as in coccidiosis and again it might be a more central location as illustrated by molluscum contagiosum. The occurrence of such dispositions of parasitic multiplication within the cytoplasm can be assumed to indicate especial activities or concentration of activities at such places that predispose or perhaps exclusively provide suitable environments for the consummation of infection.

It is encouraging to note that already methods are being developed and used successfully for exploring localized activities within the living cell. These methods, chemical and physical, may be exemplified by the histochemical studies of Dustin [13] whose results suggest that the vital staining, by such basic dyes as neutral red, of cytoplasmic vacuoles belonging to the Golgi zone or those newly formed, may be the consequence of the existence of small quantities of ribonucleoproteins within these vacuoles; or, by the illuminating qualitative and quantitative microspectrometric studies of Caspersson and his colleagues which relate the nucleus and nucleolus to the cytoplasmic protein-forming system of the cell.[14] Other newer micro methods applicable to studies of intracellular localization include use of the electron microscope

and the radioautographic technic. By the application of these and other technics to be devised we shall sooner or later begin to learn something about the nature of the internal cellular environment and its differentiation with respect to support of parasitic infection. Conversely parasitic infections of cells might be useful tools in such cytological explorations.

During the past century and with accelerating speed, analyses of biological materials have placed in the hands of scientists a number of identified and purified agents that influence profoundly physiological activity in one way or another. Enzymes, hormones, and vitamins are examples. In analytical research the parasitologist, in a broad sense, has identified pathogenic agents in great abundance and variety. He has learned to isolate them and cultivate them in pure strain. If he has not succeeded in enabling them in some instances to reproduce themselves on dead media, he has endeavored and often succeeded in purifying them in quantity by physical and sometimes by chemical means. In the case of those that multiply only in living cells he has often provided suitable living media in the form of new and unaccustomed hosts available for laboratory investigation. But, as with the biochemist, the pharmacologist and physiologist, he has not yet been able to delve deeply into the other element of the equation of biological activity namely, the living cell with which the agents react. It is one thing to know an inciting agent of a set of biological processes, quite another and a much more complex one to understand the medium with which the agent must interact. Cytology indeed has progressed, but it lags far behind the analysis of activators.

After reviewing progress of cytology during the past three quarter-centuries Schrader [15] has recently summed up the situation as follows: "It is taking no great risk to predict that 1950 will mark the end of a period, just as sharply as did 1925 and 1900 (in the progress of cytology). Whether he is pleased or not, the cytologist of the next quarter-century will find his co-workers in the laboratories of the biochemist and biophysicist. . . . Moreover, it is already obvious that in this newer alliance the cytologist will not play the subsidiary rôle that he has had in the recent past, for it is on the foundations constructed by him that this building of the future will arise." In similar vein it may be said with equal appropriateness that in the future the co-workers of the parasitologist will be found in the laboratories of the biochemist, the biophysicist, the cytologist and the pathologist, all bringing their energies and tools to bear upon that enigmatic and ultimate biologically active system—the cell. In this broadly coöperative research the agents provided by the parasitologist, the protozoa, bacteria, rickettsia, and viruses, which can be introduced into appropriate cells to loose there a series of reactions, should prove of great usefulness in attempts to discover the structure and capacities of cells. Any knowledge thus gained would have additional value for the pathologist who is seeking to understand the chain of events underlying infection and the full explanation of therapeutic benefits to be derived from chemical and immunological interventions.

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THE NEWER ANALGESIC DRUGS; THEIR USE AND ABUSE *

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ALTHOUGH morphine has been regarded for over a hundred years as the most effective and reliable compound for the relief of the more severe grades of pain, the drug has many undesirable properties. It produces respiratory depression; it increases the activity and tone of the smooth muscle of the gastrointestinal, biliary, and urinary tracts, causing constipation, spasm of the gall-bladder and bile ducts, and urinary retention; it frequently causes nausea and vomiting; and it may induce itching of the skin. If morphine has to be administered over a long period of time, tolerance to the analgesic effect develops so that the dose must be increased from time to time to obtain adequate pain relief. Under such conditions of prolonged use, physical dependence on the drug develops. The euphoria induced by morphine, although likely a desirable action which may be necessary for pain relief, leads to the abuse of the drug by persons with susceptible personalities, resulting in addiction.

Because of these undesirable actions, a constant search has been carried on for drugs which would be equal to morphine in analgesic action but which would have fewer side effects, and particularly for drugs which would have less addiction liability. Little progress was made until 1939 when Small, Eddy, Mosettig, and Himmelsbach [1] issued a summary of their studies on methyldihydromorphinone, or metopon, a new member of the morphine series of drugs which appeared to possess some distinct advantages over morphine. Since 1939, two new potent analgesic drugs, which are not chemically related to morphine or to each other, have been discovered. These are meperidine, or demerol (ethyl l-methyl-4-phenylpiperidine-4-carboxylate), and methadon, or amidone (6-dimethylamino-4-4-diphenyl-3-heptanone). The discovery of both these drugs must be credited to the German chemists and pharmacologists of the I. G. Farbenindustrie.[2] The chemical dissimilarity of metopon, methadon, and meperidine is shown in figure 1. The fact that, despite the lack of chemical resemblance, meperidine and metopon have much in common pharmacologically with each other and with morphine is rather astonishing and has given great impetus to the search for more effective analgesics. We can expect the development of new compounds in the meperidine and methadon series which may possess advantages over the original drugs; and other analgesic drugs with molecular structures differing from any yet known may be discovered. While this quest for new

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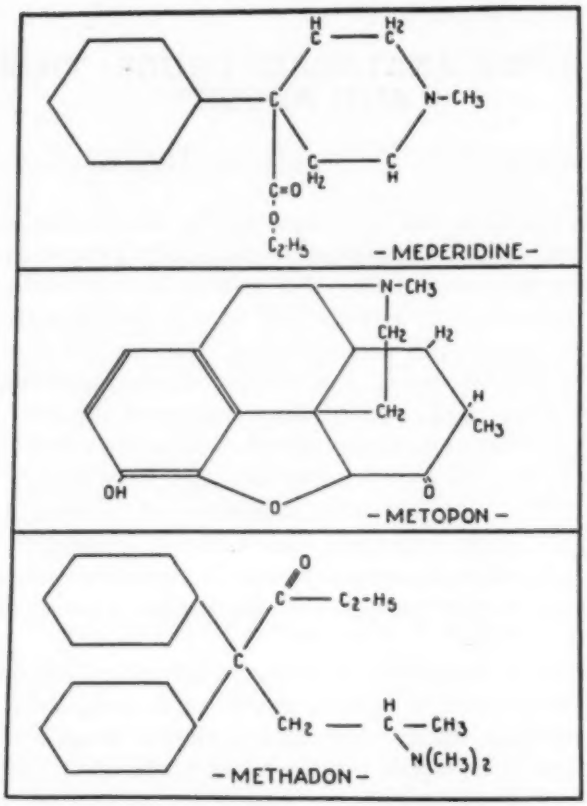

FIG. 1. Structural formulae of the new analgesics.

substances with pain-relieving actions is desirable, it will also bring confusion. The choice of an analgesic drug may soon be as complex as the choice of an hypnotic drug. It therefore seems wise at this point to attempt to assess the advantages of the three new analgesics, metopon, meperidine, and methadon, to consider their addiction liability, and to describe or discuss some indications for their use.

ANALGESIC EFFECT

Since the presence of severe pain which cannot be relieved by simpler means is the major indication for the administration of any of the potent analgesic drugs, an understanding of the mechanism of relief of pain by these drugs is important in their use. Wolff and his collaborators [3] have developed a theory of analgesia which states that the pain-relieving effects of the opiates, or similar drugs, are due to a combination of three factors: (1) elevation of the threshold for perception of pain, (2) an alteration of the emotional reaction to pain, and (3) the production of sedation and sleep. Elevation of the pain threshold and the production of sedation and sleep

appear to be less important than alteration of the emotional reaction to pain. If morphine is given after the experimental production of pain in human subjects, the pain threshold is not elevated and yet the pain is relieved.[8] Since most patients who receive morphine have experienced pain prior to administration of the drug, elevation of the pain threshold is probably of minor importance in clinical practice. Relief of pain is not necessarily associated with the production of sedation and sleep. The barbiturates, though powerful sedative and hypnotic drugs, are not effective analgesics. Most of the pain-relieving action of the powerful analgesics must, therefore, be ascribed to a rather specific alteration in the emotional reaction to pain. A person with severe pain who receives a dose of morphine, or some other potent analgesic drug, may continue to perceive the pain, but, since the pain seems to have lost its dangerous quality, the patient disregards it and, under the hypnotic influence of the drug, drifts off to sleep. It seems reasonable to assume that the alteration of the emotional reaction to pain by the analgesic drugs may be associated with the euphoria produced by these compounds. The exact sites and mechanism of action of these drugs within the central nervous system are not yet understood, but the fact that patients who have had prefrontal lobotomy for the relief of pain continue to perceive pain but are not disturbed by it, suggests that the important effect of altering the reaction to pain may be mediated through an action on the cortex of the frontal lobe.

TABLE I

Comparative Efficacy of Single Doses of New Drugs in Altering Various Factors Concerned in Analgesia

Drug	Dose Mg.	Elevation of Pain Threshold	Alteration of Reaction to Pain	Sedation	Duration of Clinical Relief of Pain-Hours
Morphine	10	2	2	1	4 Hours
Metopon	6	1	1	3	4 Hours
Meperidine	100	4	3	2	3 Hours
Methadon	5–10	3	4	4	4–10 Hours

The figure 1 indicates the most effective of the four drugs in producing the effect noted; the figure 4 indicates the least effective of the four drugs.

The comparative efficacy of the three new analgesics and of morphine in altering the factors concerned in analgesia is shown in table 1. With the exception of the elevation of the pain threshold, which has been measured, the comparisons represent the personal opinions of the author, and were assigned on the basis of experience with all the drugs. The table shows that morphine and metopon are the two most effective drugs and that meperidine and methadon are less effective. However, if the drugs are used every four to six hours, the order is radically altered. Methadon is a slowly acting,

cumulative drug and, when repeatedly administered, exerts an effect on the reaction to pain equal to that produced by morphine and excels morphine in sedative and hypnotic effect. Methadon is, therefore, not a good drug for pre-anesthetic medication and is only fairly effective in situations requiring very rapid relief of pain, but it is a very good drug for the relief of chronic pain. Under conditions of repeated dosage, methadon is equal to morphine and metopon in inducing analgesia. Meperidine, though fairly effective, is not as reliable or as potent an analgesic as are the other three drugs.

Other Pharmacological Actions

Metopon. In minimal analgesic doses, metopon is less likely to produce sedation and mental dullness than is morphine.[4, 5, 6] While respiratory depression is less marked after the administration of metopon than after the administration of morphine,[1] metopon, in conjunction with inhalation anesthetics, may produce serious respiratory depression [5] and is, therefore, contraindicated as pre-anesthetic medication. Metopon is almost as effective in relieving pain when given by mouth as when administered hypodermically.[1, 4, 5] Due to difficulties in manufacture, metopon is about 10 times as expensive as morphine, and the amount available for use may always be limited.[4]

Meperidine. Meperidine is said to produce serious respiratory depression less often than does morphine.[7, 8, 9] This statement seems to be based on clinical impressions or on counts of respiratory rate and not on actual measurements of respiratory minute volume. Nausea and vomiting are also claimed to occur less frequently than after morphine. If, however, one compares the figures published by Batterman [7] on the incidence of nausea and vomiting after meperidine with those of Lee [5] on the incidence of nausea and vomiting after morphine, it would appear that nausea and vomiting occur more often after meperidine than after morphine. Batterman gives the incidence of nausea after parenteral administration of meperidine to hospitalized patients as 8.4 per cent and the incidence of vomiting as 3.8 per cent; Lee found that the incidence of nausea after the subcutaneous administration of morphine was 3.5 per cent and the incidence of vomiting was 2.3 per cent. Despite these figures, it is common clinical experience that persons who cannot tolerate morphine because of nausea may tolerate meperidine. In man, meperidine relaxes spasm of the smooth muscle of the gastrointestinal tract [7, 10] and the ureter.[11] Although the rôle of the spasmolytic action of meperidine in relieving colicky pain has been over-emphasized, the drug at least does not increase spasm of smooth muscle as does morphine. Meperidine does not produce constipation. It is effective when administered by mouth, but is more expensive than morphine.

Methadon. Methadon is very similar to morphine in all its pharmacologic actions.[12, 13, 14, 15, 16, 17] It depresses respiration as much as does morphine,[16] causes nausea and vomiting just as frequently,[16] and is constipating

It is quite irritating when injected subcutaneously, and, if injected repeatedly into the same sites, causes severe inflammation and induration of the skin.[18] Nausea and vomiting occur so frequently after oral administration that the drug cannot be used by this route.[16]

Addiction Liability

The danger of addiction is one of the most important matters which must be considered in evaluating the proper use of a new drug. Drug addiction can be defined as the abuse of a drug to such an extent that the individual has lost the power of self control with reference to use of drug, and to such an extent that the individual or society is harmed. Himmelsbach and Small [19] have described addiction to the opiate drugs as consisting of three closely intertwined factors: tolerance, physical dependence, and habituation or psychic or emotional dependence. Tolerance may be defined as a diminishing effect on repetition of the same dose of a drug. Physical dependence refers to an altered bodily state brought about by repeated administration of a drug which necessitates continued use of the drug to maintain physiological normality. Physical dependence is manifest by the appearance of a characteristic illness when the drug is withheld. Habituation means psychic or emotional dependence on a drug—the substitution of the use of the drug for all other aims and objects in life. The extent to which these various factors are involved in addiction varies with the person and with the drug. Physical dependence has, in the past, been regarded as the most important quality of an addicting drug. Emotional dependence, however, is now believed to be the most important characteristic. It is the quality responsible for the initiation of addiction. A person becomes addicted, not because he needs the drug to prevent the appearance of a withdrawal illness, but because he enjoyed the subjective sensations the drug produces. Addicts who have been withdrawn from drugs repeatedly relapse to the use of the drug because they desire the pleasant effects of the drug and the relief of psychic or emotional stress which it brings, and not because they need the drug to relieve symptoms of a withdrawal illness. In assessing addiction liability one should, therefore, give the greatest weight to the habituation liability of the drug in question.

Tolerance

Tolerance develops to many actions of metopon,[5] methadon,[18] and meperidine,[7, 20] including the sedative and emetic effects, and the pain threshold-elevating action (figure 2). Partial tolerance to the respiratory and circulatory effects probably occurs. Tolerance to the clinical analgesic effects of all three drugs develops more slowly than does tolerance to the analgesic effect of morphine.[4, 5, 6, 7, 18] The slow development of tolerance is the greatest advantage these drugs possess over morphine. Metopon has one further advantage: tolerance to the clinical analgesic effect of metopon is abolished

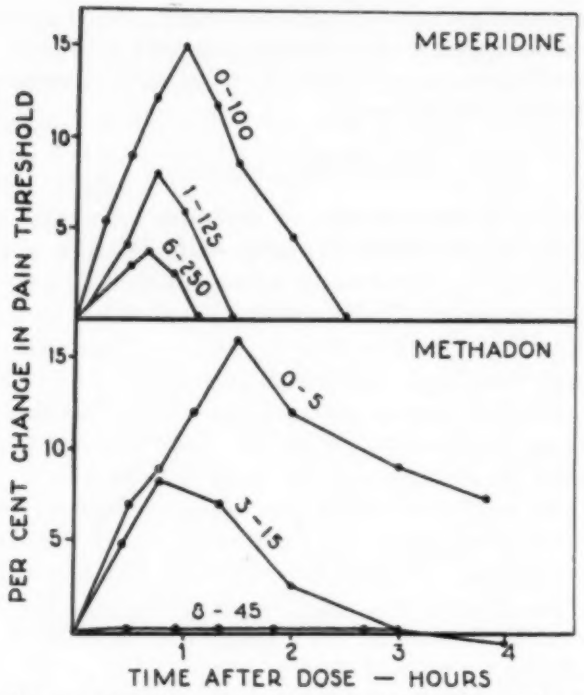

FIG. 2. Development of tolerance to pain threshold-elevating action of meperidine and methadon during addiction to either drug. Ordinates: per cent change in pain threshold calculated from the pre-dose thresholds. Abscissae: time after dose in hours. The first figure above each curve represents the week of addiction in which the curve was obtained. The second figure above each curve represents the dose of the drug being administered at that time. Note the decline in the response as addiction proceeds.

by withdrawing the drug for only eight to 14 hours.[5] This rapid loss of tolerance has not been shown to occur with any other analgesic drug.

PHYSICAL DEPENDENCE

Metopon, meperidine, and methadon all have physical dependence liability. When metopon [21] or meperidine [22] was substituted for morphine, signs of the abstinence syndrome were partially, but not completely, suppressed. Following withdrawal of metopon or meperidine after substitution for morphine, abstinence syndromes which were qualitatively similar to abstinence from morphine appeared very quickly.[21, 22, 23] Symptoms of abstinence also developed following withdrawal of meperidine after administration of large doses to former morphine addicts for 10 to 11 weeks,[22] or after withdrawal of metopon after 21 days or more of administration to patients for the relief of chronic painful disease.[5] Abstinence symptoms following withdrawal from both meperidine and metopon came on more rapidly, were less intense, and subsided more rapidly than did abstinence symptoms following withdrawal from morphine [5, 21, 22] (figure 3). Methadon completely relieved and

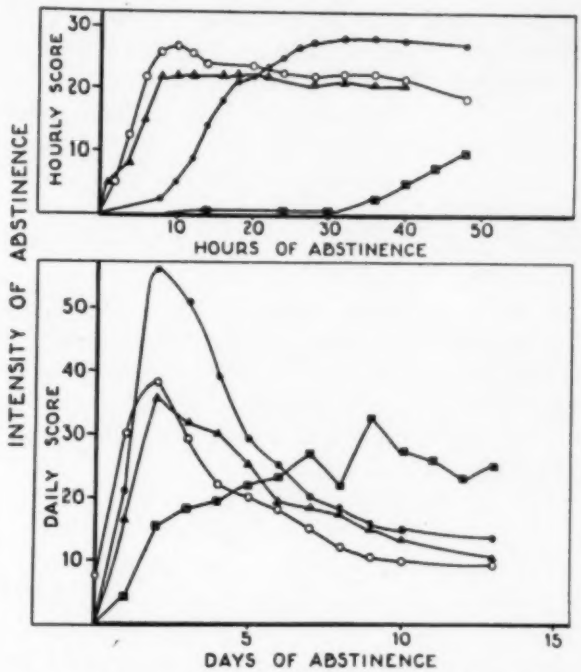

FIG. 3. Comparison of onset and intensity of abstinence after withdrawal of new analgesics. Upper curve: onset of abstinence. Ordinates: intensity of abstinence in hourly points. Abscissae: time since last dose of drug in hours. Lower curve: course of abstinence. Ordinates: intensity of abstinence in daily points. Abscissae: time since last dose in days Solid circles: abstinence from morphine. Open circles: abstinence from metopon. Triangles: abstinence from meperidine. Squares: abstinence from methadon. Both hourly and daily point scores are calculated according to the Himmelsbach [21] scoring system in which arbitrary numerical values are assigned to the various signs of abstinence.

suppressed signs of abstinence from morphine.[18] Following withdrawal of methadon after substitution for morphine, or after administration to former morphine addicts for two to six months, an abstinence syndrome developed which came on more slowly, was much less intense, and subsided more slowly than did the abstinence syndrome following withdrawal of morphine [18] (figure 3). The abstinence syndrome following withdrawal of methadon was milder than the abstinence syndrome following withdrawal of metopon or meperidine. Following withdrawal of methadon, very few of the autonomic signs so characteristic of the abstinence syndrome following withdrawal from morphine, metopon, or meperidine were observed.[18]

HABITUATION

Single minimal analgesic doses of methadon [12, 18, 24] and metopon [4, 5] seldom produce significant euphoric reaction in either non-addicts or former morphine addicts. In our experience, despite the literature on the subject,[7] single minimal analgesic doses of meperidine frequently cause mild euphoria. If, however, the drugs are administered in doses as large as one would expect

addicts to use, both metopon [25] and methadon [18] produce grades of euphoria which equal, or exceed, those induced by morphine, and which are more intense than the euphoria after any dose of meperidine. The euphoria after large doses of metopon is maintained as long as euphoria following morphine,[25] and the euphoria after large doses of methadon is sustained for 36 to 48 hours.[18] Euphoria after meperidine lasts only one or two hours. For this reason, meperidine is not as popular with experienced morphine addicts as are metopon and methadon. The behavior of men experimentally addicted to methadon was similar to that seen during morphine addiction.[18] They ceased all productive activity, neglected their personal appearances, and spent a great deal of time in bed in a semi-somnolent state. Following withdrawal of methadon, the patients complained, begged for the drug, and would take additional doses months after all signs of physical dependence had disappeared.[18] The behavior of patients addicted to meperidine is also similar to that of patients addicted to morphine.[26]

The evidence forces us to conclude that all three drugs are addicting. Any differences noted in the addiction liability of the new analgesic drugs from that of morphine are differences in degree, not kind. Tolerance has developed to actions of all three drugs. Physical dependence has been demonstrated after prolonged administration of all three drugs and, more important, all three drugs have been shown to possess considerable habituation liability.

"Natural" Addiction

Metopon and methadon have not been available for a sufficient length of time for non-experimental addiction to occur. For some time a controversy was carried on concerning the addiction liability of meperidine. It was claimed that cases of addiction had not occurred in persons not formerly addicted to morphine (so-called "primary" addicts). This view is no longer tenable since a number of cases of "primary" addiction to meperidine have been reported in the literature.[26] More than 20 persons primarily addicted to meperidine have been studied at the U. S. Public Health Service Hospital, Lexington, Ky. Their histories showed that their behavior was similar to the behavior of morphine addicts. They substituted the use of meperidine for all other aims and objects in life; they spent their savings for the drug, left their families for it, and lied and stole to obtain it. In one respect, addiction to meperidine in these cases was more undesirable than addiction to morphine. The patients used such large doses that the serious toxic effects noted by Andrews [27]—tremors, increased startle responses, and even epileptiform seizures—developed.

Clinical Applications of the New Analgesics

It is not to be expected that these new drugs will completely replace morphine. Due to its quick but long-lasting action, its reliability, its power-

ful sedative action, and its relative cheapness, morphine is still the choice for most patients requiring relief of pain for periods of less than 14 days.

The use of metopon has been restricted by the National Research Council to persons with chronic painful diseases, and the drug is available for oral use only. This decision was taken because of the slow development of tolerance to metopon, the rapid loss of tolerance on short withdrawal, the low degree of sedation, its effectiveness by the oral route, and because of the limitation of the amount available due to difficulties in manufacturing.

Meperidine seems to have lost popularity because it is not as reliable or as long-lasting an analgesic as is morphine or methadon. Severe grades of pain are often not well controlled with meperidine. The drug, however, deserves a trial in cases of pain associated with spasm of smooth muscle. It is also indicated for persons who are nauseated by morphine. Since it is effective orally, and since tolerance develops slowly, it is quite useful in managing chronic diseases associated with mild grades of pain.

Methadon can be used in most situations where morphine is indicated. Due to its slow cumulative action, it is probably not as desirable as morphine in situations demanding very quick relief of pain. The drug is useful in chronic diseases since tolerance develops slowly and physical dependence on the compound is quite mild. If a person with a chronic disease has received morphine for a long period of time, methadon is the only drug which can be satisfactorily substituted for the morphine, since meperidine and metopon do not completely suppress signs of the abstinence syndrome following withdrawal from morphine. The fact that methadon cannot be used orally is a great disadvantage, which largely limits its use to cases under hospital supervision. Due to the low intensity of the abstinence syndrome following withdrawal of methadon after substitution for morphine in cases strongly addicted to morphine, methadon is the drug of choice for treatment of the morphine abstinence syndrome.

Prevention of Abuse of the New Analgesic Drugs

Meperidine, metopon, and methadon have been placed under the provisions of the Harrison Narcotic Act in order to minimize abuse of the drugs and to limit the spread of addiction to them. Physicians should keep the danger of addiction to these substances in mind and should exercise the same caution in prescribing them as is followed in prescribing morphine. The drugs should never be used when other drugs or other measures will suffice. The dosage should be held to the minimum compatible with adequate pain relief, and the interval between doses should be as great as possible. The drugs should be discontinued as soon as the need for pain relief has passed. They should never be used primarily for their sedative actions. In chronic cases, they should be administered orally whenever possible. Self medication with a hypodermic should be discouraged. The drugs should never be given intravenously, since this method produces maximum euphoria and

carries a great risk of addiction. The drugs should not be administered to persons with known psychopathic or psychoneurotic personalities unless very definite indications for the use of a potent analgesic are present. The drugs should never be used for the relief of symptoms due to alcoholic excess, since alcoholics are very prone to addiction. The drugs should never be used for the treatment of asthma, since asthmatics are also very susceptible to addiction. It is significant that several of the cases of primary addiction to meperidine observed at Lexington, Ky., became addicted as a result of administration of meperidine for the relief of asthma.

Summary

The pharmacology, addiction liability and clinical use of three new analgesic drugs—metopon, meperidine, and methadon—have been discussed.

Metopon and methadon (in repeated dosage) are as effective in relieving pain as is morphine. Metopon produces fewer side reactions than morphine. Methadon causes just as many side reactions as does morphine. Meperidine prevents spasm of smooth muscle in man, and can often be used in subjects who do not tolerate morphine well, but it is less reliable than the other three drugs.

All three drugs are addicting. The same precautions should be exercised in their use as are followed in prescribing morphine.

Morphine remains the drug of choice for most conditions requiring quick relief of pain for short periods of time. Meperidine is indicated in cases of pain associated with spasm of smooth muscle, or in persons who do not tolerate morphine well. Metopon is limited to oral use in chronic painful diseases. Methadon can be used in most instances in which morphine is indicated. It is particularly useful in cases requiring pain relief for long periods of time, and for withdrawing drugs from patients addicted to the opiates.

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STRONGYLOIDIASIS *

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WITHIN the past few years increasing importance has been attached to the subject of tropical medicine. The truly global aspects of World War II, the return of American soldiers from far-flung corners of the earth, and the ease and frequency of intercontinental travel have all been factors leading to stimulation of interest in this subject. Although information concerning some diseases endemic in more remote portions of the world has been widely disseminated, a few, such as strongyloidiasis, have not been sufficiently emphasized. For example, McCoy [1] discusses precautions taken by the Army to prevent the introduction of tropical disease; Weber [2] reviews roentgen-ray changes seen in tropical diseases; and Sapero [3] discusses tropical disease in veterans of World War II, all without mentioning strongyloidiasis in their discussions. Attention should be given to this parasitic disease for several reasons: (1) The causative organism shows remarkable persistence in the human host; (2) The symptoms of the disease are more severe and perhaps somewhat more characteristic than common teaching would indicate; (3) The possibility of a fatal outcome is little appreciated; (4) There is increasing awareness that the disease is encountered not infrequently in temperate climates; (5) Considerable significance can be attached to the belief held by Faust [4] that *S. stercoralis* is a more recent evolutionary development among human pathogens, and because of this neither the parasite nor the host tissue as yet reacts in any fixed or regular pattern.

Probably the most important aspect of the disease is the possibility of persistence of the organism for many years following primary infection through the mechanism of hyperinfection. Consequently, many symptom-free persons who have traveled in regions where the disease is endemic are potential victims of the disease.

The case presented below is of interest for several reasons. It typifies the cases which have a long, latent period following departure from the tropics with development of severe symptoms many years later in a northern climate. The usual symptomatology of a severe infection is well illustrated, as well as the possible fatal outcome of the disease. A complete autopsy is available on a case uncomplicated by any other parasitic infestation, showing the usual findings as well as hitherto undescribed pathological changes of strongyloidiasis. Finally, the case offers an opportunity for review of the

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disease with stress on the need for consideration of the diagnosis in any person who has lived in an area where the disease is endemic.

Case Report

The patient, a 47-year-old colored male, was first admitted to the Boston City Hospital on November 20, 1945, with the chief complaint of abdominal pain. Six days prior to admission the patient had noticed the sensation of chilliness and shortly thereafter developed severe, persistent pain in the dorsum of the left foot. Four days before admission pain in the left thigh and buttock, as well as in the lower abdomen, was noted. The lower abdominal pain steadily increased in severity and radiated to the lower back. A hot, fiery sensation was present in the skin over the latter area. Marked anorexia and insomnia were present and the patient had lost 15 pounds of weight in the year preceding admission.

The patient was born in Monserrat, British West Indies, came to Boston in 1920, and lived in this area continuously, except for one brief trip to his birthplace in 1933. In September 1944 the patient had been studied at another hospital where diagnoses of strongyloidiasis and possible mediastinal cyst were made. He had been readmitted to that hospital shortly before the onset of his present illness because of severe abdominal pain, and at that time larvae of *S. stercoralis* were again found in his stool in spite of previous gentian violet therapy.

The patient was a normally developed and well-nourished male negro in considerable distress. The positive physical findings consisted of dullness over the left anterior chest and axilla, numerous small, discrete, non-tender inguinal and popliteal nodes, and moderately severe generalized abdominal tenderness.

The white blood count on admission was 5,100, differential showing two young and 36 old polymorphonuclears, 39 lymphocytes and two monocytes. No eosinophiles were seen. The hematocrit value was 34 cm. and the sedimentation rate was 12 mm. in one hour (corrected). "Living worms" were seen in the urine on admission but failed to appear in subsequent urine examinations. Large numbers of pus cells were frequently observed in the urine and occasionally red cells were seen. Stools were positive for occult blood and showed both rhabditiform and filariform larvae of *S. stercoralis*. Repeated stool cultures for bacterial pathogens were negative. The blood total protein ranged from 4.8 to 5.4 grams. Gastric analysis showed only 10 units of total acid and no free hydrochloric acid. No sickling of red cells was detected. Lumbar puncture showed normal fluid dynamics and the spinal fluid chemistry was normal. The blood Hinton and Aschheim-Zondek tests were negative.

Roentgenographic studies revealed intestinal changes interpreted as being due to diverticula of the small bowel and marked spasm of the sigmoid and descending colon. A pressure defect of the lesser curvature of the stomach with a 30 per cent gastric residue was noted on initial examination, but this finding was not confirmed on repeated studies.

Roentgen studies of the chest disclosed a mass to the left of the heart of greater density than the heart shadow and with definite notching between it and the heart. This mass was shown by lateral films to lie in the anterior mediastinum. It did not pulsate and did not compress the esophagus. A bronchogram showed no filling of the bronchioles over the mass and no filling of the left lower anterior bronchus.

Electrocardiographic studies showed a normal cardiac axis and normal sinus rhythm. T_1 and T_3 were low. These findings were interpreted as being due either to myocardial damage or to some extracardiac factor.

The patient continued to complain of severe persistent abdominal pain and steadily lost weight. He had intermittent bouts of diarrhea of five to seven soft or watery stools a day. He was treated with 2 grains of gentian violet three times a day for

10 days, and while under this therapy his stools became guaiac negative and temporarily free of larvae, but the diarrhea persisted. The abdominal pain shifted from the lower abdomen to the epigastrium. A few days later he developed marked tenderness over the spinous processes of the lower thoracic and first lumbar vertebrae and tenderness over the epigastrium. The blood hemoglobin decreased steadily and the blood smear showed a constant lymphocytosis. No increase in eosinophilic granulocytes was ever seen in the blood smear.

The consensus was that the patient's clinical findings were related to the mediastinal tumor rather than to the *S. stercoralis* infestation. He was transferred to the Surgical Service for chest exploration but refused operation and left the hospital on January 11, 1946.

He was readmitted to the hospital on February 2, 1946. During the brief interval following his discharge he had continued to suffer from generalized abdominal pain, pain in the lower back, headache, anorexia and general malaise. On the day preceding readmission he vomited large amounts of greenish material on several occasions. The morning of admission he had severe itching about the anus relieved by the application of alcohol. Bowel movements had been normal in frequency and the stools were of normal consistence. Physical findings were essentially the same as on previous admission, with the exception of slight clubbing of the fingers and more marked abdominal tenderness. The white count was normal but the number of neutrophiles had increased with a shift to the left.

Following admission the patient complained of increasingly severe abdominal pain. He took no food and very little water. His condition rapidly became worse and he died on the fourth hospital day.

At no time during the patient's course had the serious potentialities of the *S. stercoralis* infestation been considered. His clinical picture had been explained wholly on the basis of the existence of a malignant thoracic lesion with metastases.

Autopsy

A routine autopsy was performed 15 hours after death. Only the relevant pathologic findings are included.

The body was that of an emaciated, adult negro man. The mesenteric lymph nodes were enlarged to 2 or 3 cm. in diameter and were firm with a homogeneous dull yellow cut surface. A well-encapsulated, pear-shaped tumor weighing 320 grams lay in the anterior mediastinum just to the left of the midline. The apex of this tumor was at the level of the sternomanubrial joint and the base rested against the diaphragm. None of the adjacent structures were infiltrated or compressed by this tumor. On section the surface was pink, meaty and divided by thick, fibrous septa into nodules from 3 to 4 cm. in diameter. The right lung weighed 960 grams and the left 700 grams. The cut surface was dark red and large amounts of serosanguineous fluid exuded on compression. The mucosa of the tracheobronchial tree was injected and a large amount of bloody, mucoid fluid was present within the trachea and bronchi. The mucosa of the pyloric end of the stomach, duodenum, jejunum and ileum was injected. Examination of the head was restricted.

Routine specimens from the organs were fixed in Zenker's fluid and a 10 per cent solution of formalin, U.S.P. and stained with phloxine-methylene blue, phosphotungstic acid-hematoxylin and Mallory's aniline blue stain for collagen.

Microscopic Examination: Sections of the heart showed scattered filariform larvae surrounded by focal accumulations of lymphocytes in the pericardium and in the interstitial tissue of the myocardium (figure 1).

The pleura showed many filariform larvae lying in the subpleural areolar tissue and pleural lymphatics (figure 2). The alveoli contained precipitated protein, many

red cells and filariform larvae, some of which were surrounded by polymorphonuclear leukocytes, desquamated epithelial cells and lymphocytes (figure 3). The submucosal and adventitial lymphatics of the trachea contained similar parasites without any surrounding cellular infiltrate (figure 4). Parasites were present in the sinuses of the tracheobronchial lymph nodes.

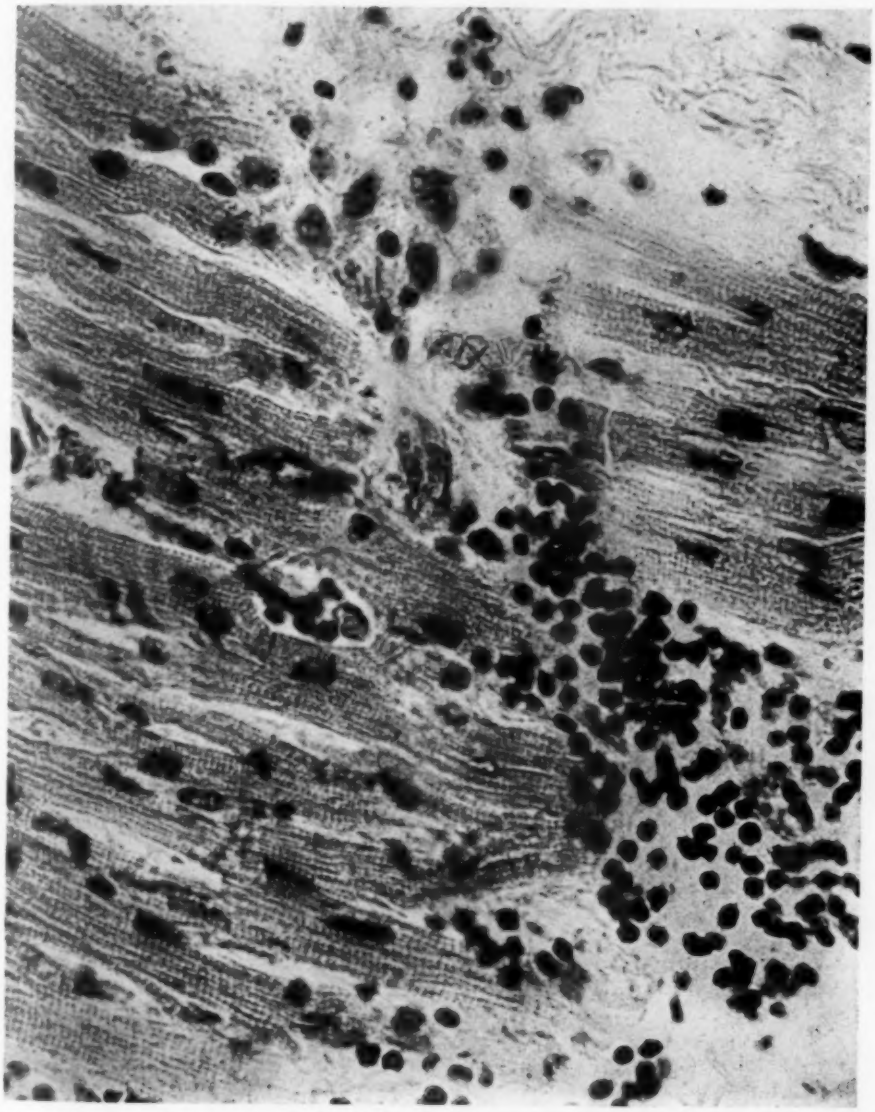

FIG. 1. Photograph of portion of filariform larva in myocardium with surrounding infiltrate of lymphocytes. × 400.

Filariform larvae were found in several portal areas in the liver and were surrounded by an inflammatory infiltrate consisting of lymphocytes and a few polymorphonuclear leukocytes. Filariform larvae were also found in the submucosal and subserosal connective tissue of the gall-bladder.

The stomach and small intestine were heavily infested with parasites. In the gastrointestinal tract the mucosa showed infected areas alternating with uninfected areas. In the stomach adult worms were present in the gastric glands and a few were seen in the stroma between the glands. Ova were seen between the epithelial cells

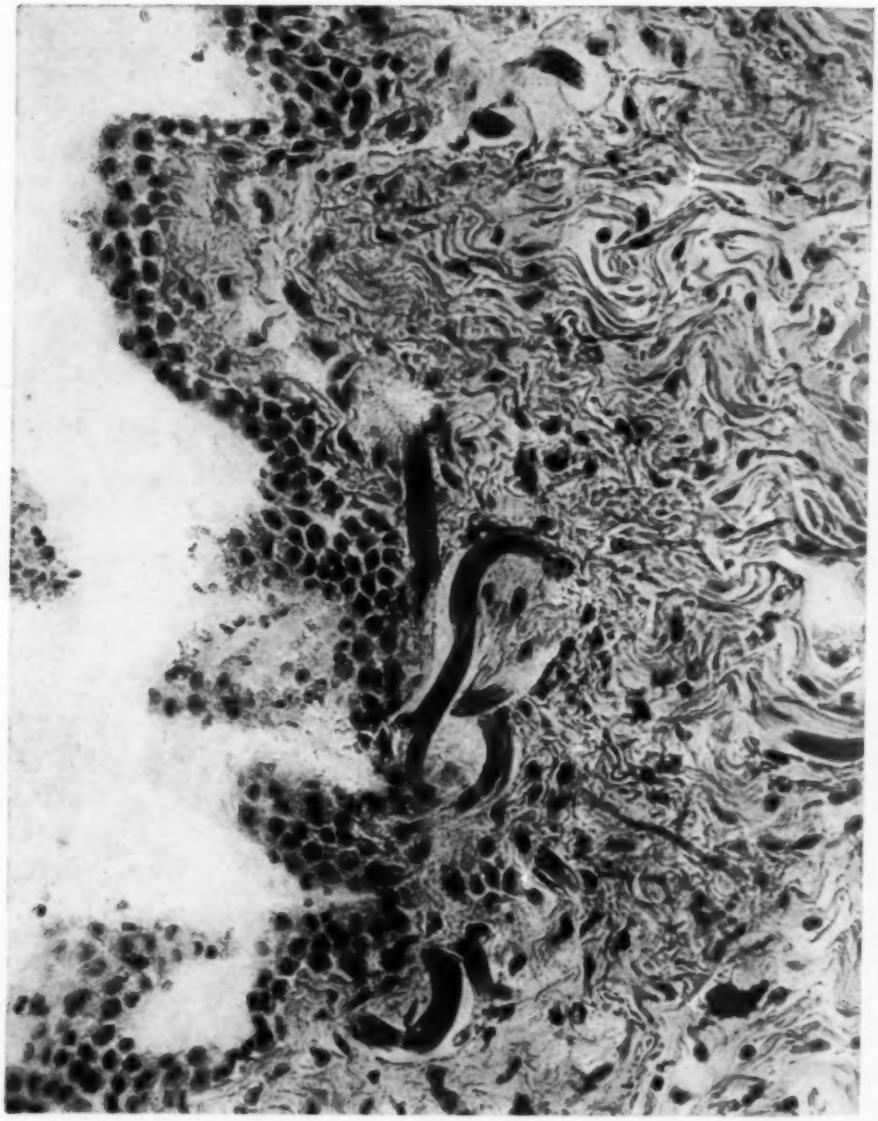

FIG. 2. Photograph showing filariform larvae lying in the subpleural connective tissue. × 300.

in the more superficial portions of the glands. The lumen of the stomach contained numerous rhabditiform larvae and adult worms and many polymorphonuclear leukocytes. No parasites were seen in the muscular layers of the stomach wall.

In the duodenum the infestation was more massive, with numerous adult worms lying deep in the crypts and in the interglandular stroma (figure 5). Some of these lay perpendicular to the long axis of the crypts cutting across several glands. In addition, ova (figure 6), embryos (figure 7) and rhabditiform larvae were present in

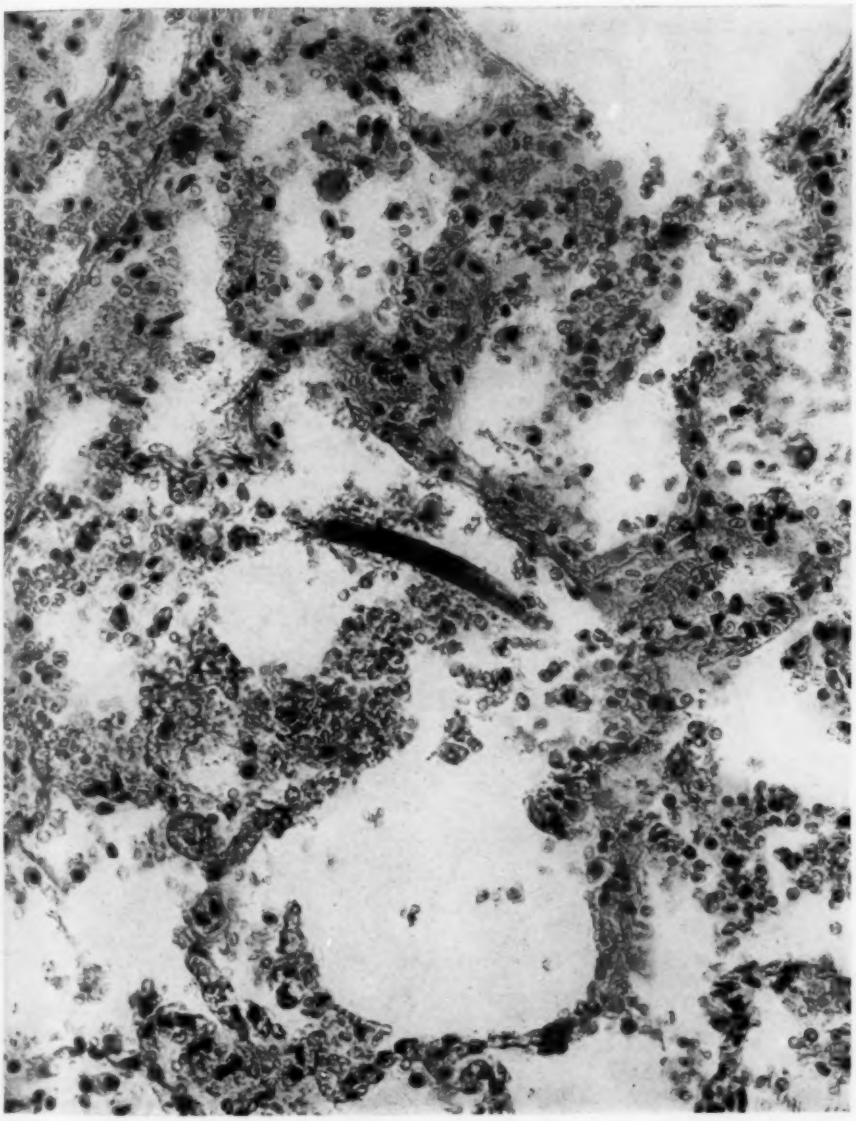

FIG. 3. Photograph of filariform larva lying in an alveolar space. Note the red blood cells scattered throughout the alveolar spaces. × 300.

the lamina propria and between the epithelial cells which form the lining of the crypts. The epithelium surrounding the adult worms, embryos and ova appeared compressed or desquamated and some of these forms of the parasite were surrounded by a mem-

brane of flattened epithelium and a zone of plasma cells and lymphocytes (figure 7). The larvae in the mucosa and the submucosa were surrounded by an exudate which differed only in that it contained moderate numbers of eosinophiles. The submucosa contained a few filariform larvae. All of the forms of the parasite were observed

FIG. 4. Photograph of filariform larvae lying in the submucosa of the trachea. Note absence of any inflammatory infiltrate. × 200.

within the lumen of the duodenum while none were seen in the muscularis or serosa.

All forms of the parasite were present in the jejunum, but fewer adult worms were noted and rhabditiform and filariform larvae were especially numerous. The latter were found in the mucosa, the submucosa, muscularis, subserosal lymphatic

and connective tissue. Many of the parasites in the submucosa and muscularis had not caused an inflammatory reaction. Several, however, were surrounded by granulomatous nodules consisting of mononuclear phagocytes, a few lymphocytes and foreign body giant cells. The larvae in the center of these lesions were densely eosinophilic. Similar nodules were found in the mesentery (figure 8).

FIG. 5. Photograph of adult female worm lying in a glandular space in the duodenum. × 400.

Filariform larvae were noted in all layers of the ileum but no other forms of the parasite were found. They were present in the lymphatics, connective tissue and fat of the mesentery of the ileum (figure 9). Most of these parasites showed no

surrounding inflammatory exudate but macrophages, lymphocytes and plasma cells were found around a few.

A few filariform larvae were found in the subserosal lymphatics of the colon and appendix and in the submucosa of the appendix.

FIG. 6. Photograph of Strongyloides ova lying in crypts and interglandular spaces of duodenum. × 400.

The mesenteric lymph nodes contained many filariform larvae in the perinodal lymphatics, the sinusoids and pulp. The sinuses contained increased numbers of macrophages, eosinophiles and polymorphonuclear leukocytes. Foreign body giant

cells phagocytizing fragments of larvae were seen in the sinusoids and pulp of the nodes.

Sections of the mediastinal tumor showed large lobules separated by dense fibrous bands. These lobules were composed of cords and clusters of spindle-shaped cells

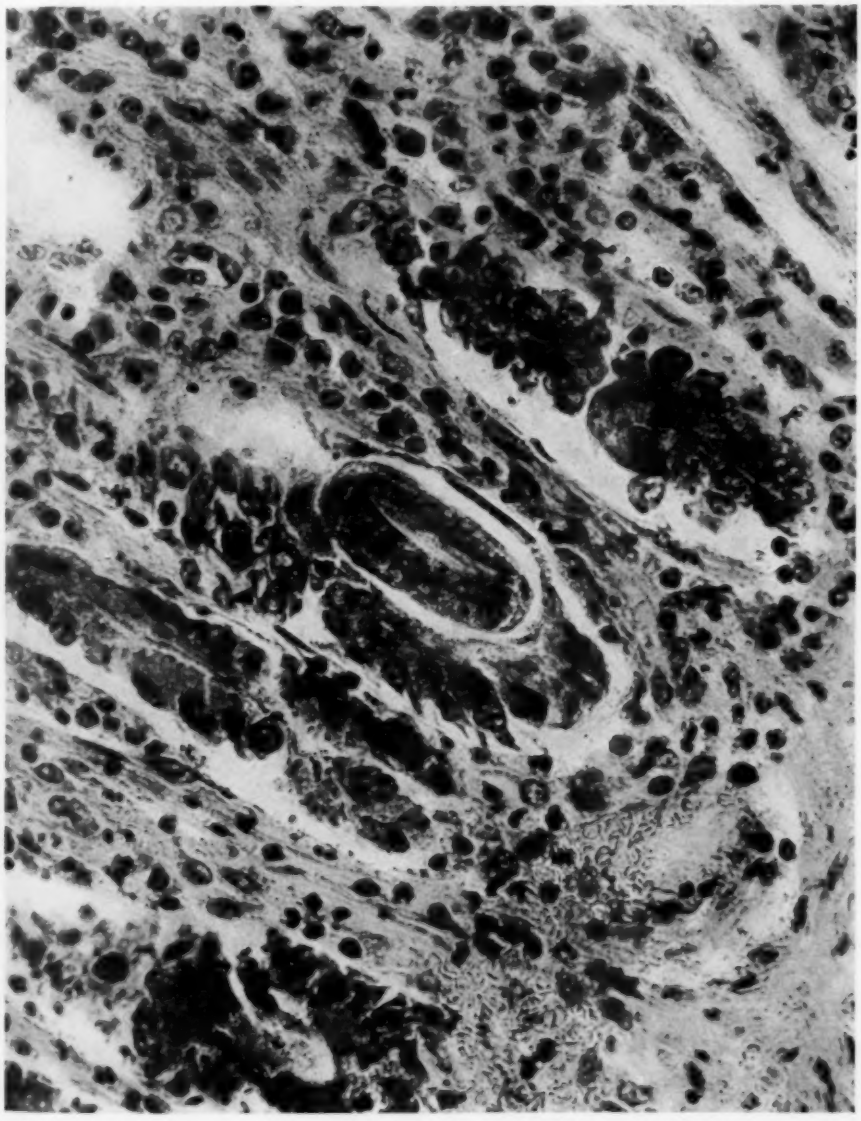

FIG. 7. Photograph of Strongyloides embryo in duodenal mucosa. Note the surrounding capsule of flattened epithelium. × 400.

with scant cytoplasm and elongated nuclei containing finely dispersed chromatin. Many of the cells were lined up around thin-walled vascular channels. The cells were uniform in appearance and no mitoses were seen.

Anatomic Diagnoses: (1) *S. stercoralis* infestation involving the stomach, small and large intestine, appendix, mesentery and mesenteric lymph nodes, lungs, trachea, heart, liver and gall-bladder. (2) Pulmonary hemorrhage and edema (diffuse). (3) Benign mediastinal tumor, ? thymoma or endothelioma.

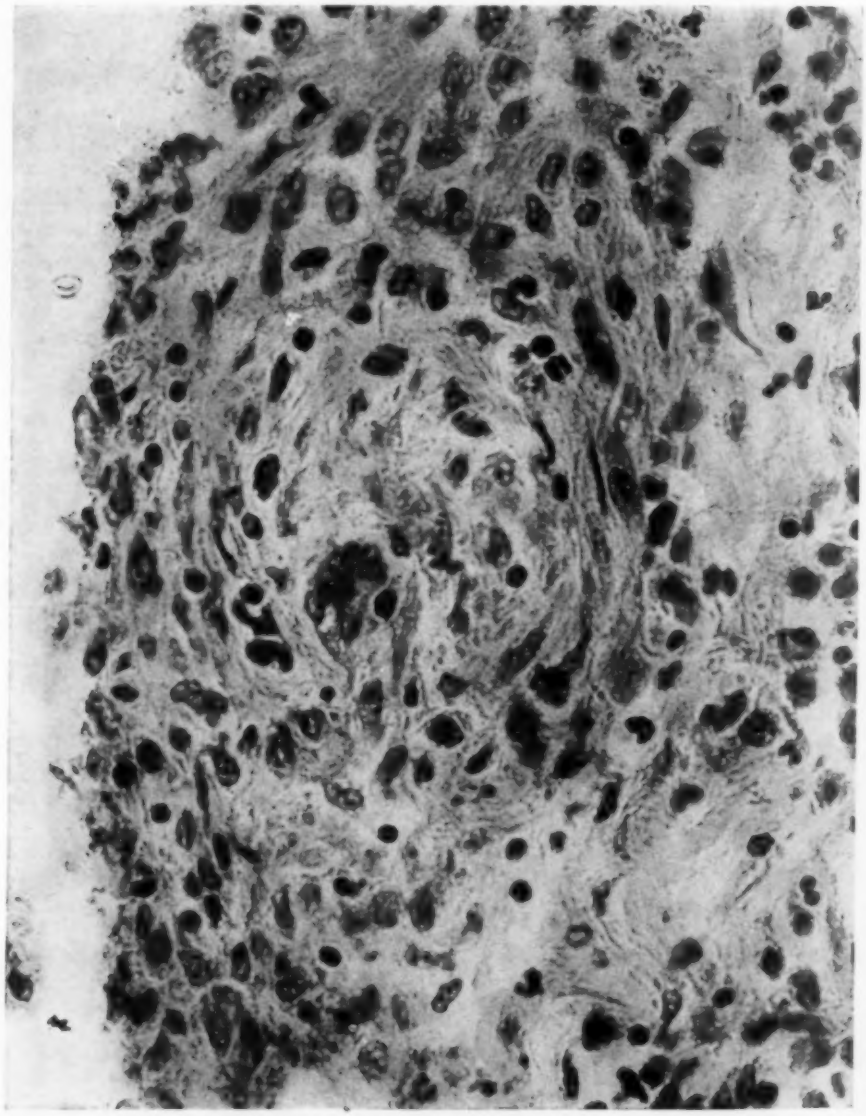

FIG. 8. Photograph of granulomatous nodule in mesentery. × 400.

BIOLOGY OF *S. Stercoralis*

Geographical Distribution. Although cosmopolitan in distribution, this parasite is much more common in warmer areas where its incidence parallels

that of hookworm. In the western hemisphere Strong [5] reports the disease as common in Brazil, Panama (23 per cent), Colombia (16 per cent) and Puerto Rico (35 per cent). In the southern part of the United States Hinman [6] found that the incidence varied from 1 to 5 per cent, while Faust

FIG. 9. Photograph of filariform larvae in connective tissue of mesentery. Note absence of surrounding inflammatory response. × 300.

found that 4 per cent of the hospital patients in New Orleans were infected. Cases of the disease are reported sporadically from more northern regions of the United States, the most noteworthy being those of Ginsburg [7] who

found a case in western Pennsylvania, and Senseman [8] who studied a patient in Rhode Island. Other cases have been reported but for the most part there have been patients who at one time lived in the tropics, or in other areas where the disease is endemic. Cadham [9] reported a case in a Canadian who had never left the vicinity of Winnipeg, but inasmuch as she was a nurse the possibility of contact infection must be considered. Shikhobalova and Semenova [10] discuss the presence of the disease in Russia and state that the climate is not incompatible with the existence of the disease. They emphasize that the infestation is most common in soldiers, many of whom spent time at the front under conditions which favored the spread of the disease.

Morphology. The ova of *S. stercoralis* closely resemble hookworm ova but are smaller, measuring 50 to 58 micra in length and 30 to 34 micra in width. They are frequently seen joined together by the remnants of the maternal uterus. They are found in the stool only during a bout of violent diarrhea or after purgation.

The rhabditiform larvae are from 200 to 250 micra in length and have a short buccal cavity leading into a double esophagus.

The filariform larvae are much longer and thinner than the rhabditoid larvae. They measure 700 micra in length and have a simple straight esophagus and intestine. Lowe and Lancaster [11] state that the tail is notched and Faust [12] found that filariform larvae in cases exhibiting the hyperinfective cycle were stunted and had notched tails. Other observers describe a sharp-pointed tail.

The parasitic females are difficult to see because of their small size and transparency. They measure 2.5 mm. in length by 30 to 75 micra in width and have a filariform esophagus one-fourth the body length. A double uterus in which ova may be seen lies in the posterior two-thirds of the body. The vulva opens on the posterior third of the body.

The adult male is shorter than the female, being about 0.7 mm. long and 40 to 50 micra wide. It has a rhabditoid esophagus and its tail is curved ventrally. In this ventral curve can be seen the copulatory spicules and the gubernaculum.

Life Cycle. The life cycle of *S. stercoralis* resembles that of the hookworm. The mother worm burrows into the mucosa of the gastrointestinal tract, produces ova by means of parthenogenesis or by hermaphrodesis (a point upon which helminthologists are not agreed) and deposits them in the crypts of the mucosa. There the ova develop into rhabditiform larvae (noninfective form) which migrate into the intestinal lumen. According to Ash and Spitz,[13] there are four variations in the cycle from this point onward.

1. The *indirect* or *sexual* cycle in which the rhabditiform larvae originating from a fertilized female are passed in the feces and develop into the "free living" females and males. These forms then copulate and the female lays ova in the feces which develop into rhabditiform larvae. The rhabditiform larvae moult and become filariform larvae (the infective form). These either penetrate the skin of the host or are ingested. After the penetration

of the skin, the filariform larvae enter the venous system and pass through the blood stream to the lungs where they escape into the alveoli and bronchi and are then coughed up and swallowed. During this passage they develop into the adolescent forms and in the alimentary canal they become adult worms and the females attach themselves to the intestinal mucosa. Under suitable environmental conditions the filariform larvae may mature and several cycles may occur outside the host.

2. The *direct* cycle in which the rhabditiform larvae are passed in the feces and develop directly in 24 to 48 hours into filariform larvae without first going through an adult phase.

3. The *direct* cycle in which the rhabditiform larvae become filariform larvae in the intestine. These filariform larvae are passed in the feces and then penetrate the skin of the perianal region immediately. This cycle is referred to by Faust as *autoinfective*.

4. The *hyperinfective* type of cycle in which rhabditiform larvae are retained for a sufficient length of time in the bowel to allow development into filariform larvae. These penetrate the intestinal wall, pass through the mesenteric lymphatics or portal system and enter the systemic circulation. They circulate through the heart to the lungs, enter the alveoli, are coughed up and swallowed, during which time they are developing into the adolescent male and female forms. In the gastrointestinal tract they develop into adult worms and the females then attach themselves to the intestinal mucosa. There is a difference of opinion among helminthologists as to the validity of this hyperinfective type of cycle. Fulleborn [14] was unable to produce it experimentally and he concluded that the soiling of the perianal skin with the patient's moist feces provided the opportunity for the rhabditiform larvae to metamorphose into the filariform stage and to enter the body percutaneously. However, Faust and his associates [15] have reported that they have produced experimental hyperinfection. Faust and DeGroat [16] have given an excellent summary of the evidence for the hyperinfective cycle, which leaves little doubt concerning its existence.

Another minor variation may occur in the life cycle. According to Faust [15] larvae may remain in the pulmonary tissue where they develop into adult worms; insemination occurs and the adult females lay ova which develop into larvae.

Length of Infestation. One of the most important characteristics of the parasite is its ability to inhabit the human body actively for prolonged periods of time. Other parasites, such as Trichinella and Echinococcus, persist in the host for long periods of time but in the inactive encysted form. Pinworm infestation perpetuates itself through the mechanism of self-reinfection of the host and thus its persistence depends on poor personal hygiene. There are many reports illustrating the occurrence of *S. stercoralis* larvae in the feces for many years after the original infection. Both Levin [17] and Bodon [18] have reported cases in which the infestation persisted for 20 years and in Palmer's [19] case there was evidence of infection over a period of 30 years.

Our patient harbored the organism for at least 13 and possibly for 26 years after leaving the presumed location of original infection. Such long-continued presence of the parasite in the human body is undoubtedly maintained through hyperinfection.

The following table shows the comparative lengths of infestation in the human intestine of the various parasites which are predominantly intestinal pathogens or which at one stage in their cycle cause intestinal symptoms.

TABLE I

Duration of Active Intestinal Infestation by Parasites

Disease	Superinfection	Average Duration	Maximum Duration
Ancyclostomiasis	0	6–12 months	6 years
Ascariasis	0	8–12 months	1 year
Diphyllobothriasis	0	years	16 years
Fasciolopsis buski (intestinal fluke) (intestinal distomiasis)	0	years	years
Oxyuriasis (Enterobiasis)	+	years	years
Strongyloidiasis	+	years	30 years
Taenia saginata	0	years	years
Taenia solium	0	years	16 years
Trichuriasis	0	1–3 months	years
Trichinosis	0	weeks	54 days
Schistosomiasis	0	10 years	13 years
Amebiasis	0	months–years	20 years

Only two parasites, *Enterobius vermicularis* and *Strongyloides stercoralis*, have a superinfective type of cycle. The intestinal infestation with Strongyloides exists for the longest period of time.

Viability. Kreis [20] has studied the adaptability of *S. stercoralis* to a changing and suitable environment outside the host and has found it to be poorly resistant to adverse conditions. The parasite cannot withstand refrigeration nor does it live long even in moist soil. In experimental studies Kreis could not recover any parasites from inoculated soil after seven days had elapsed. He points out that most species of nematodes are protected either by encystment of ova to prevent desiccation or by production of large numbers of ova to increase the possibilities of survival, but neither is true of *S. stercoralis*. However, *S. stercoralis* may maintain itself in the soil by means of a free-living cycle and in addition the mechanism of hyperinfection makes persistence outside the host less essential for survival of the parasite.

Pathogenicity. The question of the pathogenicity of *S. stercoralis* has occasioned considerable controversy. Immediately following Normand's original observation in 1876, when he attributed the so-called Cochin-China diarrhea to this organism, none questioned its pathogenicity. However, with the identification of other etiological agents as a cause for severe dysentery, enthusiasm regarding the pathogenicity of *S. stercoralis* began to wane. Darling [21] in 1911 did not believe that *S. stercoralis* caused diarrhea but hypothecated that it might make the host more susceptible to other infections.

A. L. Levin [22] in 1930 believed that symptoms resulted only in those humans whose intestine was especially suited for growth of the parasite and that the major portion of the symptomatology was due to secondary bacterial infection. Ophuls [23] believed that intestinal symptoms developed on the basis of entrance of the organism into the intestinal wall of a sensitized person. Kreis [20] in 1932 stated that in his belief dysentery could occur only with the coexistence of another parasite in the patient's gastrointestinal tract. Recent observers state that *S. stercoralis* is a true pathogen. Lowe and Lancaster [11] describe 16 cases, nearly all of recent infection, in which other parasites were eliminated following treatment, but which continued to show definite symptoms. Lewis,[24] in a study of enteric infection in soldiers, found that among the patients with strongyloidiasis were more that had symptoms than there were carriers. Of the 16 cases studied 11 had definite symptoms. Hinman [25] found severe symptoms in 85 cases and observed that the disease is one of relapses and remissions. This latter characteristic tends to modify judgment as to the pathogenicity of the organism if the patient is seen in a stage of remission. Cadham's patient [9] had no other parasites and yet showed constant and rather severe symptoms. Faust, in his extensive studies of the disease, found many patients who showed definite symptoms and some with extremely severe dysentery. Shikhobalova and Semenova [10] found definite symptoms in all of their 29 cases and I. L. Levin [26] noted that although the clinical picture was variable, the disease could be severe and even fatal. The possible fatal outcome of the disease can no longer be doubted. In the cases of Ophuls,[23] Faust and DeGroat,[16] Nolasco and Africa,[27] Gage [28] and in the case reported here no other cause for death could be found. Ginsburg,[7] A. L. Levin [22] and Hartz [29] also report deaths in patients suffering from the disease but did not show pathological evidence that *S. stercoralis* infection caused death.

Method of Infection. Undoubtedly the infective (filarial) form of the parasite most often gains entrance to the body by penetrating the skin. It is possible that infection can also occur by the ingestion of infected material, the larvae penetrating either the oral or intestinal mucosa. A. L. Levin [22] believes that this is by far the most common method of infection. During recent years increasing attention has been paid to the possibility of contact infection. Miller and his associates [30] state that this mode of infection is very common. Neal [31] describes the disease in a man who had never been in an endemic area but who had lived in close association with a group of Chinese students three years prior to the onset of symptoms. Cadham's patient may also have been infected through contact.

Pathology. The parasites enter the skin by burrowing under the scales of the stratum corneum and along the hair follicles. They then go through the deeper layers of the epidermis into the corium. Although the reaction to the parasite in the skin has not been well studied in man, certain facts are suggested from animal experimentation. The reaction apparently varies

with the number of larvae used in the inoculum. Hoeppli (cited by Faust) [4] found that with a heavy inoculation there was severe destruction of the epithelium accompanied by an exudate of fibrin, polymorphonuclear neutrophiles and eosinophiles. With a light inoculation Faust [4] found that the epidermis remained intact and that a fibrocytic proliferation occurred along the path of invasion. When the larvae remained viable, no inflammatory exudate was noted. However, many of the larvae died, underwent degenerative changes and were surrounded by a zone of polymorphonuclear leukocytes. Faust is of the opinion that this mild reaction to a light inoculation is the one which occurs naturally in the accidental infection of man. Although many parasites are arrested and die in the skin, some invade the venules of the corium and migrate to the lungs by way of the blood stream.

Upon reaching the capillaries of the lungs, the larvae break out into the alveolar spaces, producing hemorrhages within the air passages which are usually petechial but may be massive. The parasites in the alveolar spaces are usually surrounded by polymorphonuclear leukocytes, lymphocytes and desquamated epithelial cells. A severe, even fatal, pneumonitis may result. In some of Faust's experimental animals [4] the pulmonary infestation was so severe and the leukocytic response so massive that the larvae could not escape from the alveoli into the bronchi and trachea and therefore developed into the adult form in the lung. The adult females and their ova were found in the bronchial mucosa and alveoli. The larval forms then developed and the life cycle was completed in the lung. In our case the filariform larvae were found in moderate numbers in the alveolar spaces and the accompanying pulmonary hemorrhage and edema were severe and appeared to be the major cause of death. No other forms of the parasite were noted in this location. Large numbers of filariform larvae were present in the visceral pleura. It is interesting to note at this point the case reported by Froes [32] in which he found rhabditiform larvae in a hemorrhagic pleural effusion and also in the pericardial fluid at autopsy. Figure 2 shows the superficial location of the larvae in the pleura, from whence migration into the pleural cavity could be easily accomplished. The fact that the larvae found by Froes were rhabditiform suggests that the patient harbored the adults in the pulmonary tissue.

While migrating up the trachea the filariform larvae occasionally invade the submucosa and even the outer layers of the trachea as was demonstrated in our case. Although no cellular exudate was found around these parasites, hyperemia of the submucosa was evident on gross and microscopic examination.

In the gastrointestinal tract the adult females attach themselves to the mucosa of the duodenum and jejunum. Less frequently they are found in the stomach, ileum and colon. Rarely they are found in the mucosa of the appendix (Faust and DeGroat).[16] In experimentally infected animals they have been found in the mucosa of the gall-bladder. In the small intestine they burrow into the crypts of Lieberkuhn and curl upon themselves, thus

placing the genital pore near the base of the crypt. Some invade the stroma and are seen lying in the interglandular connective tissue, while others are seen lying transversely, cutting across several crypts. The adult females do not penetrate beyond the muscularis mucosae. The females deposit ova between the epithelial cells of the glands and in the interglandular stroma. These ova are most numerous near the base of the glands but they may be found in small numbers at any level of the mucosal layer. Curled up embryos and rhabditiform larvae are found in large numbers in the same locations as the ova. The epithelium of the involved crypts may be compressed or desquamated and often a thin membrane of flattened epithelium is seen encapsulating adult females, ova and embryos. The inflammatory response in the intestinal mucosa is characterized by a local eosinophilia in the areas surrounding migrating rhabditiform larvae and an increase in the number of plasma cells in the lamina propria of the involved areas. Faust [4] has shown experimentally that the removal of dead adult females is accomplished by large macrophages which gather just outside the encapsulating epithelial membrane surrounding the worm and then break through this capsule and phagocytize the parasite.

Microscopic study of a section of heavy infected duodenum or jejunum reveals a patchy loss of mucosal epithelium with numerous tunnel-like spaces in the supporting fibrous stroma. This honeycombed appearance is caused by the migration of the rhabditiform larvae from the lamina propria to the lumen of the bowel. The tips of many of the villi in the honeycombed areas become thickened and club-shaped. Rhabditiform larvae may be seen lying in the mucosal layer and Faust and DeGroat have demonstrated them in the process of penetration of the muscularis mucosae. The rhabditiform larvae change into filariform larvae in the submucosa and therefore are not found at deeper levels.

In addition to the mechanical damage caused by the parasites in the intestinal mucosa, there is a further destruction of the glandular epithelium apparently caused by a lytic agent secreted by the adult female. This is evidenced by a disintegration of epithelial cells with loss of nuclei and cytoplasmic borders, and is most prominent in the cells near the head of the adult female.

As in our case, when the hyperinfective cycle exists, filariform larvae may be found in the submucosal, muscular and subserosal layers of the jejunum, ileum, colon and appendix. Many larvae in these regions cause no inflammatory response but others produce a tubercle-like lesion. This granulomatous lesion contains a fragment of larva in its center surrounded by mononuclear phagocytic cells, lymphocytes and frequently by large foreign body giant cells. In our case these granulomatous nodules were most numerous in the lamina propria and submucosa of the jejunum and ileum. As Nolasco and Africa [27] found in their case, many of these "pseudotubercles" were adjacent to or surrounded disintegrating larvae.

Although the large bowel is not usually severely involved Nolasco and Africa reported a case in which there were small "polyps" in the cecum. These "growths" were found histologically to be small organizing submucous abscesses in connection with the base of dilated glands of Lieberkuhn.

Filariform larvae are seen in large numbers in the connective tissue spaces and in the lymphatics of the mesentery. Faust and DeGroat [16] emphasize that it is unusual to find inflammatory cells in the vicinity of the larvae. However, in our case several of the larvae in the mesentery were surrounded by a zone of macrophages, lymphocytes and plasma cells and several of the previously described granulomatous nodules were seen. Hartz' case [29] is similar to ours in this respect.

In cases exhibiting the hyperinfective cycle, filariform larvae are found in enlarged mesenteric nodes (Ophuls [23], Faust and DeGroat [16]). The larvae may be seen in the perinodal lymphatics, the sinuses and the pulp. In our case large foreign body giant cells were phagocytizing fragments of larvae in the pulp and sinuses. The sinuses were packed with macrophages, polymorphonuclear neutrophiles and a few eosinophiles. There was an increase in the amount of lymphatic pulp tissue but no hyperplasia of the germinal centers.

Filariform larvae are occasionally found in the liver [16, 27] where they lie in the portal areas. The exudate surrounding them in this location varies. Faust and DeGroat found an eosinophilic infiltrate in their case, while in ours only an increased number of lymphocytes and a few polymorphonuclear leukocytes were noted. As exemplified by our case, filariform larvae may also be found in the gall-bladder where they lie in the subserosal lymphatics and connective tissue spaces.

In a chimpanzee which died of a massive infection with *S. stercoralis*, Blacklock and Adler [33] found larvae in the pericardium. They were present in the pericardium in our case and also in the interstitial tissue of the myocardium. An infiltrate of lymphocytes surrounded them but there was no anatomic evidence of injury to the cardiac muscle fibers. As far as we can ascertain no previously reported case includes similar involvement of the heart.

Experimentally the brain and kidneys have shown evidence of invasion by larvae. Fulleborn [14] observed hemorrhages in the glomeruli and tubules in experimentally infected animals. However, in man, although parasites have been found in the urine [34, 35] parasites have not been found histologically in the kidney. Likewise Faust found brain hemorrhages in several of his infected dogs, but there has been no similar observation in the human host.

Several references are made in the literature to tumor formation in strongyloidiasis. The chimpanzee studied by Blacklock and Adler had a tumor in its cecum. This was evidently not an epithelial tumor but consisted of granulation tissue containing parasites. Berk [36] mentions the possibility of tumor formation and refers to the general discussion by Hoeppli [37]

concerning tumor formation in various kinds of parasitic disease. However, Hoeppli does not include strongyloidiasis in his discussion. The case of Nolasco and Africa presented many small "polyps" in the intestine which were shown to be small organizing abscesses and not true tumors. Our case presented a tumor of the mediastinum of questionable type. No parasites were found in the tumor and it is felt that the tumor was not related to the parasitic infection. The only "tumors" reported in the literature as attributable to *S. stercoralis* have been granulomas.

Clinical Picture. Formulation of a definite clinical pattern attributable to *S. stercoralis* is extremely difficult. Variability of location in the host and variation of host susceptibility are more marked than in any other parasitic disease. The not infrequent existence of a long latent period between infection and the development of symptoms presents a particular problem. The frequent association of *S. stercoralis* with other parasites adds to the complexity of the clinical picture. The problem can best be approached by following the path of the parasite through the body.

Within 24 hours after penetration of the skin by the infective form a marked pruritic erythema, perhaps depending in degree on the presence of previous sensitization, may appear at the site of entry. This rash is comparable in pathogenesis and appearance to the "ground itch" of hookworm. A short time later, usually within 24 to 48 hours, the larvae pass through the lungs and often give rise to transitory pulmonary symptoms. (Severe pulmonary symptoms are usually due to a hyperinfective cycle with marked and diffuse involvement of the lungs.) When the organism enters the gastrointestinal tract it finds a habitat favorable for longer survival and is able to cause more marked changes. Symptoms arising on the basis of these changes tend to be more specific but even here there is great variation in the type and degree of response with few features that aid in the differentiation of strongyloidiasis from other intestinal parasitisms. The point to be emphasized is that *S. stercoralis* can and frequently does cause severe intestinal disturbances. It is unfortunate that so many studies of the disease have of necessity been made on patients who harbored other parasites.

Certain organs other than the skin, lungs and gastrointestinal tract may become involved and give rise to symptoms. The reports suggesting infestation of the gall-bladder and biliary tract are not infrequent. The presence of renal involvement with the appearance of *S. stercoralis* larvae in the urine, as demonstrated experimentally by Fulleborn,[14] is partially paralleled in the human by a case described by Whitehall and Miller [35] who found larvae in the urine of a serviceman. However, this patient had urinary symptoms prior to his arrival in an endemic area. Faust [4] has described experimentally developed central nervous system lesions in the dog and suggests that such involvement in the human may occur and give rise to symptoms.

No clear-cut delineation of the clinical course can be made from an analysis of the reported cases. For the purpose of clarification, various

clinical findings stressed by different authors will be discussed briefly with emphasis on those that are more frequent and of greatest help in diagnosis.

Diarrhea is seen at some time during the course of all cases that are clinically diagnosed. Shikhobalova and Semenova report its presence in nearly all of their 29 cases. It may be mild or very severe.[11, 12] Although the diarrhea may be constant, it is usually intermittent. The presence of occult blood is a nearly constant finding if the diarrhea is severe, and according to Hinman [25] and Simpson [38] the stools may be grossly bloody.

Abdominal pain and tenderness have been particularly stressed by Hinman [25] and a study of other clinical reports reveals that these findings are not infrequent. In Hinman's series of 85 cases abdominal pain was the chief complaint in 44. The pain was most often generalized, epigastric or right-sided. Abdominal tenderness was present in 29 of the patients.

Constipation was found by A. L. Levin [22] to be the most frequent symptom in the average patient. It is usually mild in degree and of varying duration. Faust [12] lists constipation alternating with mild diarrhea as a frequent finding.

Pulmonary signs and symptoms have been described by Berk.[36] This author believes that *S. stercoralis* is a frequent cause of transient pulmonary infiltration and reports two cases showing such a complication. He concludes that this disease should be considered in any patient who has in addition to gastrointestinal complaints dyspnea, cough or hemoptysis. Lowe and Lancaster [11] have noted pulmonary symptoms in seven of 16 patients studied and stated that pulmonary involvement is more common in strongyloidiasis than in hookworm disease. However, in Hinman's series of 85 cases, only two had cough and signs of bronchitis. It is of interest that Gage [28] reports the recovery of the larvae of *S. stercoralis* from the sputum of a patient believed to be suffering from tuberculosis, and Froes [32] found rhabditoid larvae in the pleural effusion of his patient. Other reports suggesting pulmonary involvement are available and it appears that infestation of the lungs (especially in hyperinfected patients) is more frequent than is usually stated.

Dyspepsia was described in five of 16 carefully controlled cases reported by Lowe and Lancaster.[11] Vague abdominal distress, heartburn and gaseous discomfort are frequently associated with the disease.

Jaundice or other evidence of biliary tract involvement has been reported so frequently in association with *S. stercoralis* as to invalidate the possibility that it is an incidental finding. Eight of Hinman's patients had marked right upper quadrant tenderness and several others were admitted to the hospital with a diagnosis of cholecystitis. Levin mentions that several of his patients showed a picture of "biliary toxemia." Nisbet [39] believed that the obstructive type of jaundice in his patients was due to the presence of *S. stercoralis* organisms in the bile ducts and v. Engle [40] discussed a case with the clinical features of acute gall-bladder disease. Bodon [18] reports a case

with recurrent attacks of right upper quadrant pain, tenderness and jaundice that came to operation three times and in each instance no cause for the symptoms other than strongyloidiasis was demonstrated.

Urticaria and edema may be seen at any time during the course of the disease, and according to Simpson [38] these symptoms are not infrequent. Recurring attacks of urticaria dominated the clinical picture in Cadham's case. It is logical to assume that these allergic manifestations occur most often in the hyperinfected individual.

Vomiting was found by Hinman as the chief complaint in five patients and was a feature of the disease in two of the 11 cases reported by Miller and his associates.[30] I. L. Levin [26] described vomiting as a common symptom and Senseman [8] noted that nausea was an important symptom in his case. Nausea and vomiting are ascribed to either reflex nervous stimulation or to direct irritation of the gastric mucosa by the parasite. In the presence of vomiting the possibility of detecting parasites in the vomitus must be kept in mind.

Fever has been reported by I. L. Levin [26] as present in all of his 12 patients but this finding has received little attention from other observers. A. L. Levin [22] believes that much of the symptomatology in strongyloidiasis is due to the secondary bacterial invasion of the gastrointestinal tract. If this is correct, fever should be a more constant finding.

Colitis as mentioned by Simpson,[38] *rectal ulcers* by Wagner [41] and *urinary symptoms* by Whitehall [35] are infrequent findings and consequently are of little value in diagnosis. *Psychoneurotic symptoms* are frequently noted in association with strongyloidiasis but their evaluation is difficult.

Laboratory Findings. The degree of eosinophilia in the peripheral blood is often used as an absolute criterion as to the presence or absence of a parasitic disease. However, in all parasitic disease, including strongyloidiasis, lack of eosinophilic response is not uncommon. Although many authors, including Hinman, Shikhobalova and Semenova, and Senseman, stress the frequency of eosinophilia, others, such as Miller, Simpson and Faust, do not consider it to be a constant finding. Faust believes that there may be an early increase in eosinophiles with a steady decline as the disease becomes chronic. Further confirmation is given to this view by the investigations of Lowe and Lancaster who, in studying 16 cases of fairly recent infection, found a pronounced and constant eosinophilia. On the other hand, a review of cases that show very severe symptoms or a fatal outcome reveals that the eosinophiles are frequently not increased and are often entirely absent from the peripheral blood stream as was true in our case.

Anemia is not a striking feature but when present is of a mild hypochromic variety. It is much less constant and much less marked than in hookworm disease.

Examination of the stool, as in any parasitic disease of the intestinal tract, is of primary importance. The ova of strongyloides are rarely seen

except after severe purging. The characteristic larvae are easily overlooked but when searched for repeatedly and with care they can usually be detected. Although many methods of stool examination have been devised, for general use the simpler methods are best. Faust advocates the use of coverslip preparations, and if the stool is negative by this method concentration technics are utilized. Simpson makes a small depression in the fecal mass, places therein a small amount of water and incubates for 24 hours. The larval forms pass into the water where they can be seen with the 16 mm. objective. Lowe and Lancaster are convinced of the value of stool cultures and describe in detail the procedure. Many other methods of stool examination are described in the literature, but either the technic of Faust or that of Simpson is the procedure of choice. Confusion may arise in differentiating the larvae of strongyloides from those of hookworm, especially if the stool specimen has stood sufficiently long to enable hookworm ova to hatch. The rhabditiform larvae of *S. stercoralis* have a buccal cavity which is much shorter than that of the corresponding form of hookworm. The esophagus of the filariform larvae of strongyloides is longer than that of the corresponding stage of hookworm, usually measuring one-half the length of the body. The tail of the filariform larvae in strongyloides is often notched, according to Lowe and Lancaster, while that of the hookworm is always pointed.

Examination of duodenal washings is a very effective method of diagnosis. This procedure is of considerable value when intraduodenal medication is being given and is extremely effective in evaluating the efficacy of therapy.

Gastric analysis may reveal the presence of adult or larval forms of the parasite. Hypochlorhydria has been reported as a fairly common finding. A. L. Levin reports the presence of either achylia or mild hyperchlorhydria but Shikhobalova and Semenova found gastric acidity below normal in 9 of their 13 cases.

The search for parasites should also include studies of other body fluids. They have been identified in the sputum, pleural exudate and the urine. Vomitus should also be examined for larvae.

Roentgenographic findings in strongyloidiasis have received little attention. Garland,[42] in a discussion of tropical diseases of interest to the radiologist, mentions briefly that there may be changes in the small bowel suggesting ileitis and states that the presence of local infiltrating lesions in the large bowel has been reported. Berk [36] suggests the possibility that the "deficiency pattern" seen in hookworm infestation may also be found in strongyloidiasis.

Diagnosis. A suspicion of the presence of *S. stercoralis* might be aroused by the nature of the symptoms and a history of residence in an area where the disease is endemic. This suspicion would further be stimulated by the discovery of an eosinophilia. Confirmation of the diagnosis depends, however, on identification of the larvae in the feces or in other body excretions.

Repeated stool examinations or, if the results of stool examinations are questionable or negative, studies of the duodenal washings are by far the most important diagnostic procedures. Hinman [43] has stressed the fact that inasmuch as the female worm can produce only as many as 50 ova a day, diagnosis is dependent on the presence of a large number of females and careful stool examinations.

A practical point in diagnosis is the observation of Cordi and Otto [44] that strongyloid larvae rapidly disappear from stool specimens kept under refrigeration.

Differential diagnosis is not usually difficult. Confusion can arise when there is infestation with another intestinal parasite, especially hookworm. Not only are the cutaneous, intestinal and pulmonary findings similar, but also the larval forms of both parasites resemble each other closely. Their differentiation has been discussed above. As emphasized by Strong [5] examination of a freshly passed stool usually shows the ova of hookworm and the larvae of *S. stercoralis*. With intense diarrhea the oval forms of both parasites may be passed, but if the stool is allowed to stand for a few hours the ova of *S. stercoralis* will hatch. If there is any real doubt concerning the identity of the parasite, culture of the stool for several days will result in the development of the adult forms of *S. stercoralis*.

The finding of an acute surgical abdomen has been reported frequently in strongyloidiasis and affords a problem in differential diagnosis. Levin [22] reports 12 cases and states that three of the patients came to operation. Symptoms related to the biliary tract or to the appendix most often result in such surgical intervention.[18, 8]

Strongyloidiasis should be excluded when dealing with pulmonary lesions —especially those of subacute or chronic nature. *S. stercoralis* has been definitely implicated as one of the causative agents of pulmonary infiltration. Other parasitic diseases which may cause similar changes are discussed by Berk.[45] He mentions *Ascaris lumbricoides, Endameba histolytica, Fasciola hepatica* and *Necator americanus*. Tuberculosis has been reported by Gage,[28] chronic bronchitis by Hinman [25] and bronchopneumonia by Barlow [46] as being erroneously diagnosed when the pulmonary lesions were in fact caused by *S. stercoralis*. Careful study of the sputum in such cases may simplify the diagnosis.

Rare localization of the parasite in the host raises other differential problems. Pericarditis, pleural effusion and renal symptoms have all been attributed to *S. stercoralis*.

Treatment. The treatment of strongyloidiasis is far from satisfactory. Simpson [38] points out that a failure to appreciate the truly pathogenic nature of the parasite has resulted in a lack of interest in the development of more effective therapeutic agents. There is also a tendency to reason falsely that since *S. stercoralis* is an intestinal parasite, any good vermifuge will satisfactorily eliminate the organism. It is obvious that a non-absorbable drug

will not affect the pulmonary lesions. It is also true that in the intestine the deeply embedded females may be difficult to eliminate by the usual vermifuges. The disappearance of the larvae from the feces is not a good index of the efficacy of the therapy, for as pointed out by Faust [47] even in non-treated cases the larvae disintegrate while passing through the bowel and there is a gradual decrease in the egg production of the female worm. There is also the possibility that in the hyperinfective cycle larvae can leave the intestine prior to the institution of therapy and return by way of the lungs after cessation of oral medication.

Although, as in all parasitic diseases, many drugs have been used, gentian violet is by far the most popular. Faust introduced the oral use of the drug in this country in 1930 and has been its strongest advocate. In 1932 [12] he reported cures in 45 of 47 cases and more recently he has stated that it frequently eradicates the disease.[48] Faust administers one grain three times a day for a total of 50 grains (16⅔ days), repeating the course if necessary.[49] Hinman [43] reported good results with dosages of one grain three times a day for from 7 to 10 days. He did not conduct follow-up examinations. Simpson [38] raises considerable doubt concerning the effectiveness of the drug, pointing out that the stools may be free of the parasites and yet the infection persist in the body. Although Lowe and Lancaster [11] treated 13 patients with two courses of oral gentian violet, only one patient was considered cured after careful follow-up study. Lewis [24] found that of 10 patients diagnosed and treated overseas only one was considered cured upon return to the United States. In our case there was an initial disappearance of the larvae from the stool but they reappeared before the course of therapy had been completed.

The administration of gentian violet by stomach or duodenal tube has received increasing attention. V. Engle [40] reports cure by the use of a 1 per cent solution of gentian violet in a patient unaffected by previous oral medication. He noted that nausea and vomiting were frequent when the drug was given in large doses. Faust [50] gave 25 c.c. of a 1 per cent solution to 10 patients unaffected by oral medication and reported complete cures in all. He also found vomiting to be of frequent occurrence and suggested that slow administration of the drug by Murphy drip might lessen this toxic symptom. More recently Denhoff [51] reports failure of this method of therapy in five patients.

In 1936 Wagner [52] suggested the use of intravenous gentian violet therapy in patients with the violent hyperinfective form of the disease. Faust [48] recommends a similar method of treatment of foci outside of the gastrointestinal tract and states that 25 c.c. of a 0.5 per cent solution will be well tolerated. Palmer [19] reports a patient with *S. stercoralis* larvae in the stools who was treated by intravenous gentian violet after oral use of the drug proved ineffective. The patient died of another disease and at autopsy

no evidence of *S. stercoralis* infestation could be found. However, Lewis [24] failed to effect a cure by this method. It appears that this method of administration is worthy of further trial in cases with severe symptoms or when there is evidence of hyperinfection.

There are no contraindications to the use of gentian violet. Following oral medication there may be mild nausea and vomiting and the urine occasionally becomes violet. The vomiting which follows intraduodenal installation of the drug may be alleviated by lessening the speed of administration. Faust [48] has mentioned the possibility that medication with gentian violet may modify the indirect or hyperinfective cycles of the disease into the direct type but points out the epidemiological value of such a conversion.

Simpson [38] maintains that iodine solution given by duodenal tube is very effective and warrants more general use. He gives the drug as follows: the patient receives a saline purge one hour before supper and omits breakfast; 4 c.c. of compound tincture of iodine is introduced into the duodenum on alternate days until neither the feces nor the duodenal washings show any parasites or ova. An apparent value of this technic is the necessity for making the endpoint of therapy dependent on examination of the duodenal washings.

A number of other drugs have been tried and of these only thymol and dihydronal (heptylresorcinol) have any possible value.[9, 38, 41] Fuadin, emetine hydrochloride, tartar emetic and many other drugs have proved to be entirely ineffective.

The evaluation of any form of therapy has in the past often depended on the absence of larvae in the stools. However, the examination of stools is an unreliable index of cure. Faust [49] considers his patients cured only after repeated negative stools, studied by concentration methods, for three to six months after therapy. Lowe and Lancaster [11] consider a patient cured when he is symptom-free, has a normal eosinophile count and when cultures of his stools taken three times at weekly intervals are negative for *S. stercoralis* parasites. Simpson [38] considers that the only real evidence of cure is the absence of ova and parasites from the duodenal washings, and Denhoff [51] offers concrete evidence to support this consideration.

In summary, for the treatment of early or mild cases oral gentian violet is worthy of trial in dosage of one grain three times a day. The drug should be administered in enteric coated capsules with a one and one-half hour coating. Even if the disease is not cured, this treatment often leads to symptomatic relief. If oral medication does not prove effective, intraduodenal administration with either gentian violet or tincture of iodine should be attempted. In a patient showing severe symptoms or evidence of hyperinfection intravenous gentian violet is indicated. Twenty-five c.c. of a 0.5 per cent solution can be given on alternate days for four doses. Search should be continued for more effective therapeutic agents.

Summary

A fatal case of *Strongloides stercoralis* is presented. The filariform larvae were found in the usual locations and in addition were found in the myocardium, lungs, trachea, liver and gall-bladder.

The clinical manifestations of this infection are variable but in general they include abdominal pain, alternate diarrhea and constipation, cough, dyspnea and hemoptysis.

Treatment with various drugs produces variable results. The best treatment to date is probably found in the use of gentian violet, given orally at first. If the infection is not cured by oral administration, intraduodenal and possibly intravenous administration should be tried.

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THE ELECTROCARDIOGRAPHIC RESPONSE TO CHANGES OF POSTURE DURING RESPIRATORY ARREST FOLLOWING DEEP INSPIRATION OR EXPIRATION: CLINICAL SIGNIFICANCE *

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In earlier studies [5, 6] the simultaneous effect of changes in posture and certain respiratory phases on the electrocardiograms of healthy persons and cardiac patients was reported. Distinct differences in the three standard leads of the electrocardiograms were observed in both groups. These observations have been confirmed.[3, 14] These studies have been extended in the present work by including the use of chest leads. In addition, experiments on dogs have been made in order to further interpretation of the results obtained in man.

Procedure

Electrocardiograms were obtained on 65 healthy persons of both asthenic and pyknic builds and on 116 cardiac patients without congestive heart failure. Among the cardiac patients were 20 with valvular disease, 32 with coronary disease, 45 with myocardial disease, 10 with essential hypertension, five with nephritis and hypertension, and four with hyperthyroidism.

Electrocardiograms were taken in the recumbent position (*a*) during normal respiration, (*b*) in respiratory arrest after maximal inspiration (period I) and (*c*) in respiratory arrest after maximal expiration preceded by maximal inspiration (period E). The subjects were then requested to stand for 15 minutes. At the end of this period while the subjects remained standing electrocardiograms were again obtained in the manner described above. The subjects then resumed the recumbent position and electrocardiograms were obtained at intervals during normal respiration.

Three standard leads and usually two chest leads were used at the fourth intercostal space at the left border of the sternum (C_2) and a little outside the apex in the fifth intercostal space (C_4) with the right arm as the indifferent electrode. Slipping of the electrode was prevented by bandages. The

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The majority of these investigations have been made in the Research Laboratories of the Department of Psychiatry, Illinois Neuropsychiatric Institute, with the collaboration of members of the Department of Medicine, University of Illinois. The author wishes to thank Dr. Francis J. Gerty, Head of the Department of Psychiatry, and Dr. Warren S. McCulloch, Director of Laboratories, Illinois Neuropsychiatric Institute, and Dr. Robert W. Keeton, Head of the Department of Medicine, University of Illinois, for their aid. Several of these investigations have been made in the Physiology Laboratory of the George Williams College of Chicago, and the author is indebted to Dr. Arthur Steinhaus, Head of that Laboratory for his coöperation.

electrocardiograms were taken by string galvanometer (Cambridge type), Grass, Offner, or Siemens Halsky's amplifiers.

A careful analysis of the data revealed that only three electrocardiograms are required for diagnostic purposes, namely: in the recumbent position during normal respiration, in the standing position in period E after the patient has been standing for 15 minutes, and again in the resumed recumbent position during normal respiration.*

Evaluations of the changes in the S–T segment and in the T-wave were made in Lead I, Lead II and chest leads. Changes of the final deflection in the third lead have been generally neglected.

The Effect of Posture and of Respiratory Arrest after Deep Inspiration and Expiration on the Electrocardiograms of Healthy Persons

Recumbent Position. In period I (respiratory arrest after maximal inspiration) the R-waves in Lead I were decreased; in Lead III they were slightly increased. The T-wave in Lead I and occasionally in Lead II and in the chest leads was lower or nearly iso-electric: at the same time, a bradycardia occurred.

In the next phase, period E (respiratory arrest after maximal expiration) the R-waves in Lead I were increased and in Lead III were decreased. The T-waves in Leads I and II and in the chest leads were definitely increased in height. These T-waves were sometimes even higher than those in the recumbent position under normal respiration, and were accompanied by tachycardia.

Standing Position. Similar electrocardiographic pictures and variations in the heart rate developed in the two respiratory periods as in the recumbent position, but these changes were more pronounced. The T-waves which were usually already slightly lower during the standing position in normal respiration became iso-electric or slightly negative in period I. However, in the following phase (period E) an increase of the T-waves in Leads I and II and in the chest leads similar to those in the recumbent position were observed.†

The electrocardiograms after the subject resumed the recumbent position (normal respiration) showed the same pattern as the original record (figure 1).

The Influence of Posture and of Respiratory Phases on the Electrocardiograms of Cardiac Patients

The Recumbent and Standing Positions. Changes in the R-waves and heart rate during the various respiratory phases were similar to those found

* For reasons of economy, only these phases of the electrocardiogram are reported here. The intermediate steps are in my original publication.[5]

† In order to study whether a time element is involved in these responses, some healthy persons were requested to stand for an hour, then the electrocardiograms were taken in the same manner, but the results were the same as those taken after the 15 minute phase.

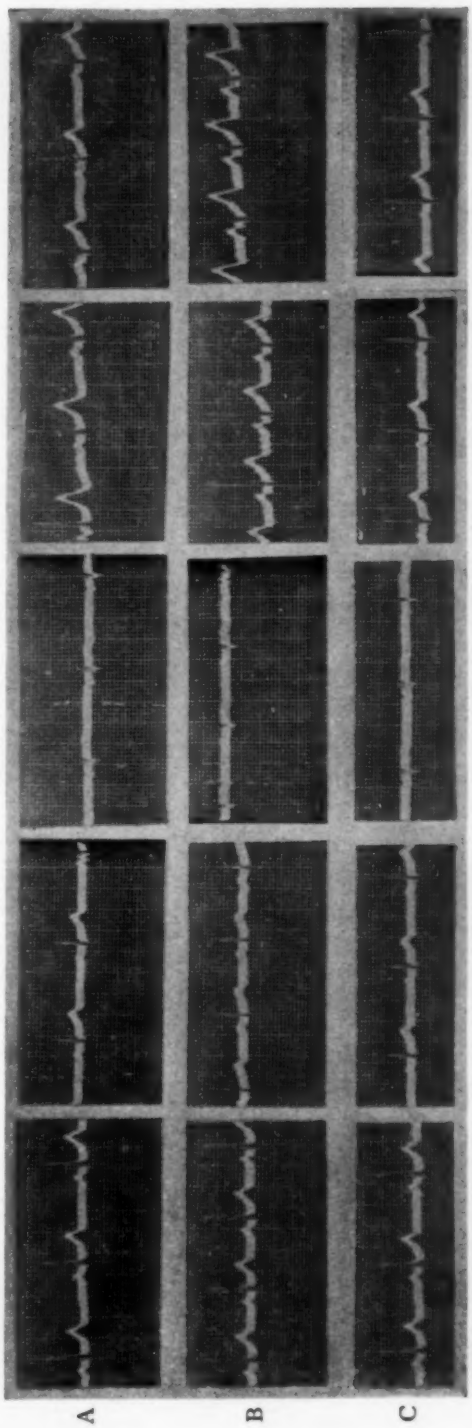

FIG. 1. From left to right I, II, III standard leads. C_3 chest lead, C_4 chest lead. A, electrocardiogram in the recumbent position during normal respiration; B, electrocardiogram in standing after deep expiration and C, electrocardiogram in the resumed recumbent position (during normal respiration). Healthy person, 31 yrs.

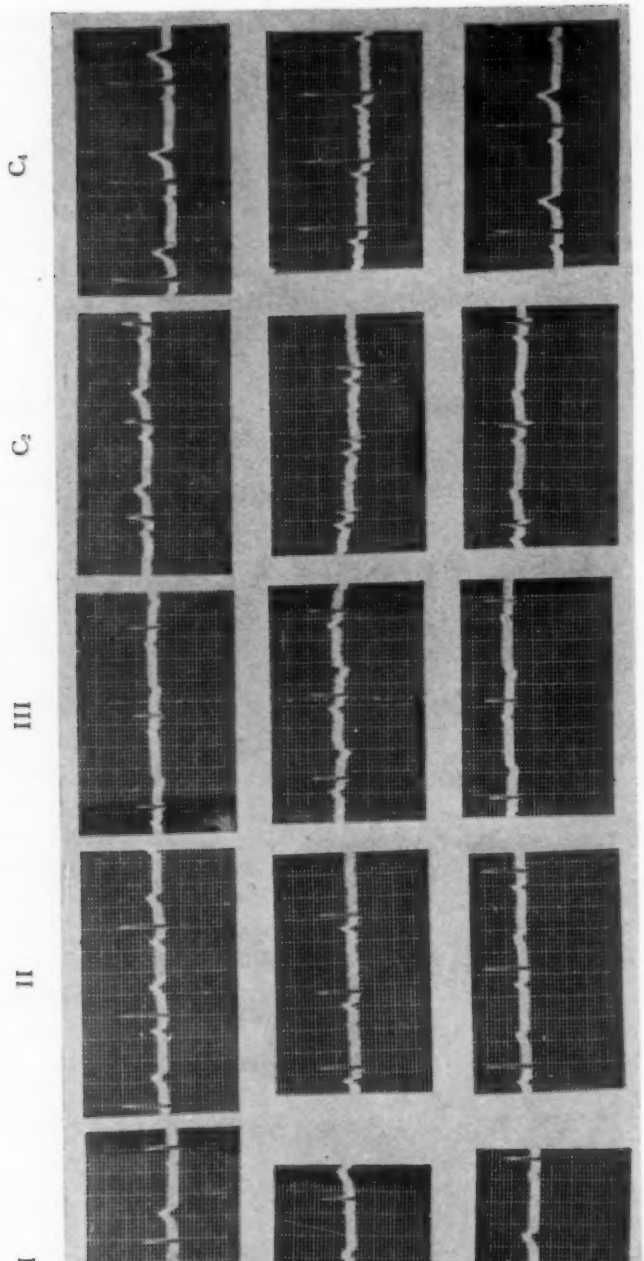

FIG. 2. Leads as in figure 1. A, B, C as in figure 1. B. T., 26 yrs. Mitral valvular disease, compensated.

in healthy persons. The alterations in the final deflection in period I were likewise similar, but the changes of the final deflection in period E in the erect posture were completely different from those of healthy persons in this phase. There could be differentiated two kinds of responses.

In 80 per cent of those cardiac patients in whom T-waves were normally positive and of slightly lower voltage in the recumbent position, changes in the electrocardiogram in standing position in period E were observed. These T-waves became iso-electric or slightly negative in Lead I, Lead II, both, or in the chest leads. Sometimes depressed S–T segments were seen

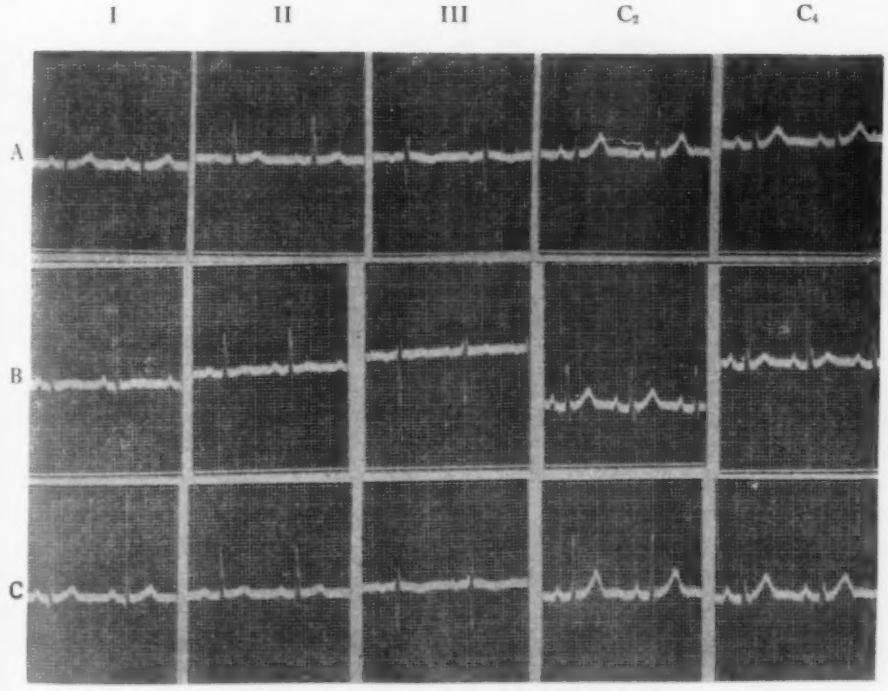

FIG. 3. Leads as in figure 1. A, B, C as in figure 1. I. D., 41 years. Essential hypertension (160/116), compensated.

in these leads. Under these conditions patients with valvular disease or hypertension, for example, showed pathological electrocardiograms, where these appeared normal when taken in the recumbent position (figures 2 and 3).

In another group of patients in whom the final deflection was already pathological in the recumbent position during normal respiration, a previous negativity of these T-waves became more marked. Some S–T segments which were previously depressed showed further depression in Lead I or Lead II or in some chest leads in period E in the standing position. Sometimes the pathologic changes in the final deflections in the chest leads were

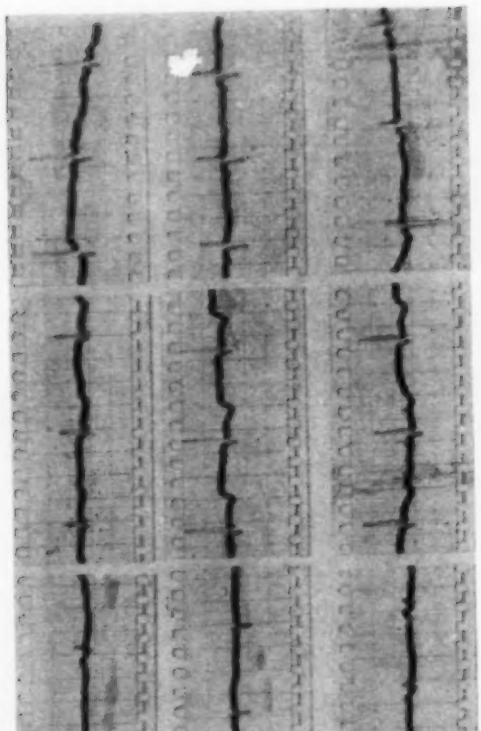

FIG. 4. Again leads as in figure 1 and A, B, C as in figure 1. I. S., 61 yrs. Essential hypertension (200/112), compensated.

more pronounced than in the standard leads. About 60 per cent of the second group showed such alterations (figure 4).

In the resumed recumbent position the original normal electrocardiogram reappeared immediately in the first group (apparently patients with slight cardiac damage). In the second group of patients in whom the original electrocardiogram showed pathologic tracings, the changes in the final deflection which had occurred during the standing position disappeared more slowly, sometimes requiring 10 or more minutes.

Discussion

First of all, it was necessary to determine whether extracardiac factors such as changes in skin resistance, changes in the electrical axis due to the diaphragm variations, changes in the tone of the sympathetic and vagus nerves, and changes in the blood pressure were involved in the electrocardiogram response of cardiac patients to postural changes in the respiratory phases.

Skin-resistance. It might have been possible that the electrodes had slipped a little after keeping them on the skin for a long time during the different procedures. Examination of the skin resistance during all of the above-mentioned stages revealed no change.

Change in the Electrical Axis Due to Change in the Position of the Diaphragm. As is known the diaphragm descends greatly during a deep inspiration in the recumbent position, during normal respiration in the standing position, and especially during deep inspiration in the standing position. At the same time, changes in the form and size of the heart take place. But these postural and respiratory changes in diaphragm and heart are completely counteracted by the maximal expiration. This was proved by careful roentgen-ray investigations in normal persons and in cardiac patient.[5] During full expiration in standing the electrical axis is the same as during normal respiration in recumbency, as checked by roentgen-ray and electrocardiogram. It might again be emphasized that this phase (period E) is of importance for the evaluation of postural and respiratory changes in the electrocardiogram. It is clearly necessary that diaphragmatic excursion be unimpaired.

The Vagal and Sympathetic Tone and the Blood Pressure. In healthy persons and cardiac patients a slowing of the heart rate and a lowering of the blood pressure as well as a slight lowering of the T-waves (in Lead I or II or in one of the chest leads) occur during period I in the recumbent position. Similar changes are found in both groups of persons in period I in the standing position, but here the alterations in the T-waves are more pronounced so that they become iso-electric. This together with the bradycardia suggests a rise in the vagal tone since experiments of Rothberger and Winterberg on dogs [12] and my experiments on cats [7] have demonstrated that an increase in vagal tone is accompanied by a considerable decrease in the height of the T-waves.

During period E, healthy persons in recumbent and standing positions have an increase in heart rate, an increase in the height of the T-wave and a rise in the blood pressure up to the previous level. These changes point to an increase in the sympathetic tone, since Rothberger and Winterberg have found in dogs that a rise in sympathetic tone is associated with an increase in the height of the T-wave.* It seems probable that central pulmonary cardiovascular reflexes [7] are elicited through these maximal respiratory efforts.

By maximal inspiration a great amount of blood is sucked into the chest due to the great increase in the negative intrathoracic pressure. This blood pools temporarily in the enlarged pulmonary vascular bed during the inspiratory phase, stimulating sensory pressor-receptors in the pulmonary blood vessels and eliciting pulmonary cardiovascular reflexes analogous to those from the carotid sinus.

In cardiac patients similar pulmonary cardiovascular reactions (slowing in heart-rate and lowering of the blood pressure accompanied by lowering of the T-wave in period I) can be observed. However, as it was described, the electrocardiograms of many of the patients do not show an increased T-wave in period E in standing position despite the increase in heart rate and blood pressure.

Cardiac Factors. Apparently not extracardiac, but cardiac factors are responsible for the difference in electrocardiographic reactions between normal and cardiac patients. According to Mayerson,[17] the cardiac output is decreased in the standing position as compared to the recumbent position because of the diminished venous return and the pooling of the blood in the veins of the extremities in the erect posture. Such a diminution in the cardiac output must affect the coronary blood supply since the magnitude of the cardiac output is one of the main factors in the proper filling of the coronary arteries. Thus, some degree of anoxia is produced in the heart muscle from diminished coronary circulation in all persons during the standing position. In healthy persons, this diminished coronary blood supply seems to be of no significance in period E in the recumbent and upright position because of the compensatory effect of extracardiac factors (increase in the sympathetic tone, rise in blood pressure, rise in intrathoracic pressure, etc.). But, in cardiac patients in whom the heart muscle is pathological or in patients in whom the coronary circulation is already in some way reduced by coronary disease, this additional anoxia (orthostatic anemia) is sufficient to produce pathologic electrocardiographic pictures (iso-electric T-waves or inversion of the T-wave in Lead I or II or in the chest leads, depression of the S–T segment in these leads) as in anoxia from other causes. These electrocardiographic alterations are similar to those found during the anoxemia test [8] or in the exercise test.[2]

* It might be mentioned that Nordenfeldt and Wendkos have also shown alterations of the T-waves due to preponderance of either vagal or sympathetic tone.[10, 19]

Our observations are also in agreement with findings of Bartlett [1] who tried to induce physiologically myocardial ischemia on a tilt table. He considers this method as a test for circulatory efficiency for the selection of pilots and the diagnosis of coronary disturbances.

Experiments on Dogs

Some experiments on dogs have been performed in order to investigate the influence of posture on the electrocardiogram of these animals and seem to support our observations on patients.

Experimental Procedures. Electrocardiograms with three standard leads were taken on 22 dogs under nembutal anesthesia in lying position, after 15 or more minutes in a tilted position of 90° (head up) and again in the recumbent position. The animals were tied on the animal board, the electrodes held firmly by bandages. The effects of the following procedure on the electrocardiographic response in different positions were also investigated: excision of the carotid sinus and the vagi and intravenous injections of various drugs (histamine, atropine, nitrites, aconite).

Results. In brief there were no great variations in the electrocardiogram after repeatedly changing the position except under very deep anesthesia. These findings are in agreement with the observations of Mayerson that tilting dogs from the horizontal to the upright (head up) position does not provoke any considerable cardiovascular embarrassment.[17]

Clamping the carotid sinus on one or both sides did not interfere greatly with the electrocardiogram in the lying or the standing position. The same was seen after cutting the vagi to eliminate the aortic depressor nerves.

Intravenous injections of histamine, atropine or nitrites did not induce considerable change into the electrocardiogram during postural changes but nitrites in doses (intravenously 33 mg. $NaNO_3$/kg.) sufficient to produce a great fall in blood pressure affected the electrocardiogram of the dog in the standing position very strongly. If the dog was kept for only a few minutes in the upright position, ventricular fibrillation occurred and the dog died despite immediate return to the supine position and intravenous injection of adrenalin (figure 5).

Further, in another series of experiments different doses of aconite extract were injected subcutaneously in order to produce an artificial myocardial damage. Injections of 0.6 c.c. into a dog of 8 kg. were followed by a bradycardia and a lowering of the T-wave in Leads I and II. In the upright position, pathological electrocardiographic patterns with increased QRS intervals and iso-electric T-waves appeared. The bradycardia was much more pronounced, and the respiration stopped after the animal was kept 10 minutes in the upright position. Return to the lying position did not change the electrocardiographic picture and the other pathological signs, and the animal died a few minutes later (figure 5).

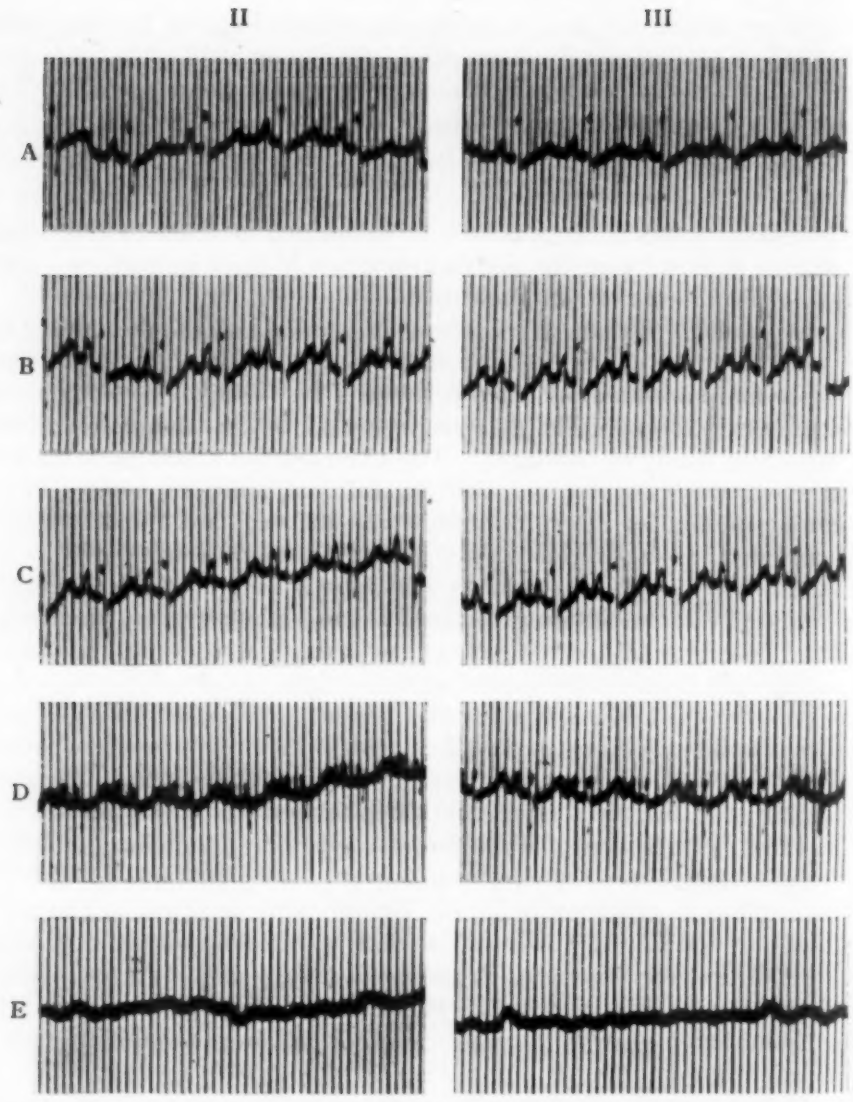

FIG. 5. Lead II, Lead III; A, electrocardiogram on recumbent position; B, electrocardiogram on standing 15 minutes; C, electrocardiogram in the resumed recumbent position; D, the electrocardiogram in the recumbent position after injection of 33 mg. $NaNO_2$ per kg.; E, electrocardiogram in standing (after 2 minutes). Note ventricular fibrillation. Dog 10 kg. Slight nembutal narcosis.

These experiments seem to demonstrate that severe anoxia of the heart produced by great diminution of the cardiac output and of the coronary blood supply due to nitrites will provoke pathological cardiovascular responses of the dog in the upright position, whereas the lying position is not accompanied by this reaction. Further, a myocardial damage which was apparent and well tolerated in the lying position might become manifest

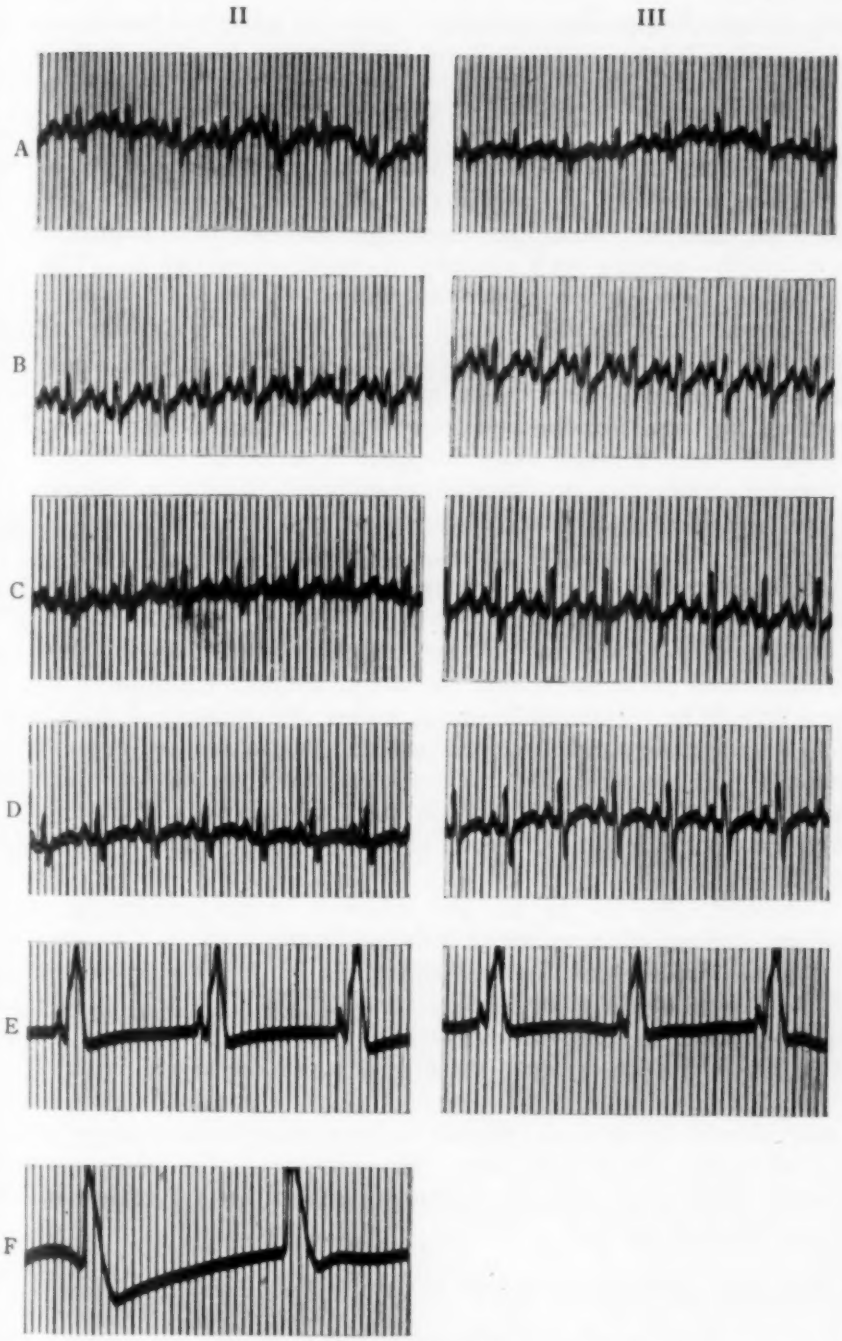

FIG. 6. II, III as in figure 5. A, B, C as in figure 5. D, electrocardiogram in the recumbent position after subcutaneous injection of 0.6 c.c. aconite extract. E, electrocardiogram in the standing position. Note the pathological electrocardiographic changes. F, electrocardiogram in the recumbent position again. Note the changed pathological electrocardiogram in Lead II. Dog 8 kg. Slight nembutal narcosis.

during the standing position and might critically affect the heart as seen in the myocardial damage of the dog due to aconite.

Conclusions and Clinical Significance

First, it should be emphasized again that in healthy persons of both asthenic and pyknic builds, alterations in the electrocardiogram, especially in the final deflection, take place during period I in the standing position. But in healthy persons such changes disappear in period E. This point seems to have been overlooked by some workers.[15]

In contrast, many cardiac patients show pathologic electrocardiographic changes in period I and further in period E in the upright position. In one group of patients who did not show any pathologic electrocardiogram in the recumbent position, pathologic changes appeared in the final deflection in period I on standing and did not disappear in period E.

Similarly, pathological electrocardiographic changes in persons with myocardial defects or coronary disease were aggravated in period E during standing position. Such alterations (depressions of S–T segments and isoelectric or inverted T-waves) were observed in Lead I or II and in the chest leads.

The clinical observations and the results of animal experiments suggest that deficiencies in the function of the heart (due to myocardial or coronary disease) might be revealed in a simple manner by the method described.

This test can be carried out without imposing a burden on the heart of a patient. On the other hand, some accidents have been reported which occurred during exercise test and during anoxemia tests.[4, 11, 18] (Just recently there appeared two reports of fatal accidents during the exercise test.[9, 13])

Moreover, some insight into the nature of heart block can be obtained by electrocardiographic records in different positions.[16]

It seems that the described method might be of some prognostic value. The electrocardiographic alterations observed during standing in patients with myocardial disease vanished quickly on resumed recumbency if the disease was mild, but slowly if the disease was more severe.

It might be added that in some conditions of postural hypotension and in neurocirculatory asthenia, similar electrocardiographic changes might be observed in the standing position. However, these conditions are accompanied by other symptoms (i.e., fainting, dizziness, etc.) so differential diagnosis can be made easily.

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HYPERTENSION AS A REACTION PATTERN TO STRESS; SUMMARY OF EXPERIMENTAL DATA ON VARIATIONS IN BLOOD PRESSURE AND RENAL BLOOD FLOW *

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There has long been an awareness of a relationship between life situations, emotions and the level of blood pressure in normal and hypertensive subjects. Moreover, it has been suspected that such pressor effects have relevance to the pathogenesis of essential hypertension but the connection has not been established. The present investigation was undertaken in an attempt to explore this possibility.

Thus far investigations of this relationship have proceeded chiefly along one of two lines. O'Hare in 1920 demonstrated experimentally among hypertensive subjects significant pressor responses during what he called "excitement" induced, for example, by a discussion of members of the subject's family.[1] He provided no data concerning the personalities of the subjects or the nature of the conflicts involved. On the other hand, Moschcowitz [40] had already observed that extreme cautiousness, paucity of fantasy life and inability to "enjoy themselves" were traits characteristic of hypertensive patients. Further and more detailed personality studies of subjects with essential hypertension have been accomplished by Alexander,[2] Saul [3] and Binger et al.[4]

Attempts to induce hypertension experimentally in animals have led to the emergence of two theories of pathogenesis: "neurogenic" and "humoral." It is becoming increasingly likely from the accumulating data that both mechanisms are operative in a synergistic way in essential hypertension.[5] In this regard the recent report of pyopagus twins with communicating blood vascular systems is significant. One had a relatively sustained hypertension and the other a labile blood pressure which occasionally rose to hypertensive levels.[41] Through Goldblatt's work [6] interest has become focused on the circulation of the kidney and on humoral products of renal ischemia. Recently a vasoexcitor material has been identified by Shorr [7] and his coworkers in dogs with temporarily impaired renal blood flow from shock. This material they found also in the blood of human subjects with essential hypertension.[8] The method of measuring renal blood flow in the intact human subject developed by Homer Smith [9] and his associates has allowed of a study of the relationship of emotional reaction, blood pressure and renal blood flow in man.

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Smith [9] demonstrated in man during sudden fright a pressor effect associated with reduced renal blood flow similar to that induced by injection of epinephrin. Visscher, in animals, has shown that stimulation of the sympathetic nerves to the kidney is likewise followed by blood pressure elevation.[10] Shorr and his co-workers have noted among hypertensive dogs sharp rises in the concentration of vasoexcitor material when samples of blood are drawn by unfamiliar workers or under other circumstances of stress.[11] Recently Ferris [12] has added new data to this accumulating body of evidence that either or both neural and humoral mechanisms may be involved during stress and in association with emotional conflict. He found, by blocking sympathetic impulses with tetraethyl ammonium bromide (T.E.A.), that the ultimate level of blood pressure (T.E.A. floor) varied with the state of relaxation and security of the subject. While it was high during periods of anxiety it was found at lower levels during relative serenity. The difference in blood pressure level after neural block with T.E.A. he attributed to the activity of circulating humoral agents.

Whatever the inferences which can be drawn concerning the pathogenesis of essential hypertension, it is clear that the distribution of circulating blood in the hypertensive is vastly altered. He has less blood flowing through the kidneys and other splanchnic areas, less through the skin and more through the skeletal muscles than do non-hypertensive subjects.[13, 14] As Cannon has pointed out, the cornered man or animal whose arterial pressure is elevated is mobilized for fight or flight.[15]

Method

Fifty-eight hypertensive subjects who had a resting-seated diastolic blood pressure repeatedly and consistently 100 or higher were picked at random from the patients of the New York Hospital. None gave evidence of vascular anomaly or primary renal disease from urinalysis, pyelograms, urea clearance and concentration tests. They were considered to have "essential hypertension." This group was compared to 42 non-hypertensive healthy individuals and 150 subjects with vasomotor rhinitis and bronchial asthma. The clinical course of the subjects was closely followed over a period of one to three years and at the same time their personalities, attitudes, habits and general behavior were studied in detail under a variety of circumstances.

Twenty-one of the 58 hypertensive subjects were subjected one or more times to measurements of renal blood flow. Fifteen of the normal subjects were similarly studied. The procedure followed was essentially that outlined by Goldring and Chasis.[16] Sodium para-amino hippurate was utilized for measurement of effective plasma flow. Inulin, determined chemically by a modification of a method described by Hubbard and Loomis,[17] and mannitol, determined by the method of Corcoran, Lowenstein and Page [18] were utilized for the measurement of glomerular filtration rate. The subjects were all adequately hydrated prior to the experiment and urine was collected by

catheter. The total time of the experiment varied from 120 to 150 minutes and was divided into collection periods lasting 15 to 20 minutes each.

After two or three control periods during which the subjects were lightly entertained and diverted and the environment was maintained as neutral as possible, topics involving significant personal conflict were abruptly introduced into the conversation. This discussion was then carried on for two periods lasting 30 or 40 minutes. At the end of this time the subjects were strongly reassured and attempts to promote relaxation and diversion were undertaken for the remaining periods of the experiment.

Six of the hypertensive subjects were thus examined before and at varying intervals after lumbodorsal sympathectomy.

Observations

A. Relation of blood pressure level to attitude, emotions and life situation. Variations in the course of hypertension are very difficult to evaluate because usually symptoms bear little relation to the height of the blood pressure. Frequent sphygmomanometric determinations of blood pressure, however, showed major variations from time to time in the subjects followed. The variations corresponded fairly clearly with changes in the general level of security of the individual. Examples are shown graphically in figures 1 and 2.

The patient whose findings are shown in figure 1 was a 48 year old civil service employee who was discovered to have hypertension (175 mm. Hg systolic and 125 mm. diastolic) in January, 1946 when he came to the hospital complaining of a recent left facial palsy. The latter cleared up uneventfully over a period of weeks, but his hypertension persisted. Figure 1 shows the recorded variations in his blood pressure over a period of nearly two years. His mother, a strong, domineering individual, has hypertension. She expected perfect behavior of the patient, and she allowed his older brother to "boss" him. At 36, against his mother's wishes, he was married secretly to a 34 year old schoolteacher. His wife was also strict and exacting. "She doesn't believe anyone has any nerves." For the first year he continued to live at home supporting his mother rather than his wife. Finally, they set up a menage of their own, but he was never able completely to emancipate himself from his mother. His Bell's palsy and the discovery of his hypertension occurred shortly after a serious conflict between his wife and mother. After he consulted the clinic it was repeatedly demonstrated that his blood pressure fell to lower levels when he was able vigorously to ventilate his resentments against his wife. He was particularly humiliated by her failure to disclose the amount of her earnings as a schoolteacher. Finally, she was interviewed and her coöperation enlisted in an attempt to build up his confidence and support him in a frustrating situation at work where he felt that he was being discriminated against because of his affiliation

with the minority political party. Following the enlistment of his wife's support a normal blood pressure was recorded on March 4 (figure 1). He said that he had been able to "talk back to the boss and get my own way. When I see the big boss now he smiles. It seems that after each fight he smiles more. Maybe he's beginning to realize I'm not a pushover. Since I have been coming here they treat me better down at work." His blood pressure was high again, however, six weeks later following what he considered to be an arduous experience of being presented at conference and having to reveal his brother's much more favorable status, both financially and in his mother's eyes. A week later his pressure was again low in a setting of satisfaction over optimal relations with his wife. By July, 1947 the conflict between his

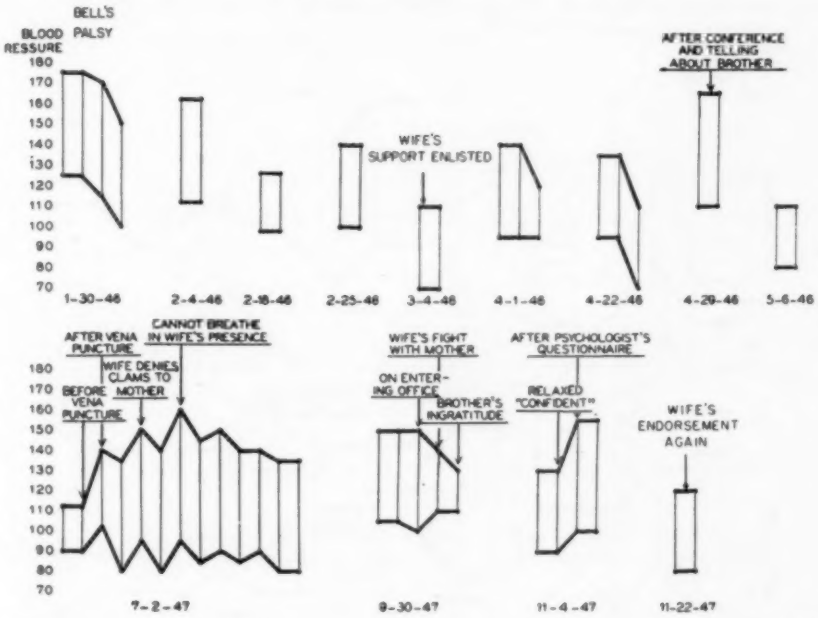

FIG. 1. Variations in level of blood pressure over a period of two years in a 48 year old civil servant. Note close correspondence of changes to status of relations with wife.

wife and mother had again become troublesome. The patient was particularly disturbed because his wife, in distributing some clams which he and she had collected, refused to give any to his mother. Even the discussion of this topic was associated with a brisk elevation of blood pressure. The problem was again dealt with as before, and finally when he felt "on top of the situation" again by November, 1947 his blood pressure was within normal range.

In figure 2 is illustrated the case of a 41 year old essentially asymptomatic hypertensive whose blood pressure elevation was also accidentally discovered at a time when he appeared for examination for promotion to public school

principal. His conflicts centered particularly about his wife who considered him socially inferior and a poor provider. Even when his blood pressure was at normal levels it could be made to rise repeatedly by a discussion of his wife (figure 2). The blood pressure could be made to fall, on the other hand, during a discussion of his vacation. He was eager to secure a Ph.D. degree in psychology and had been working on a thesis without much interest or support from his wife. She considered it a waste of time because it was not lucrative. He finally acceded to his wife's wishes and undertook a remunerative but what he considered undignified job as salesman for a toy balloon company. His blood pressure was then recorded at high levels (see October 13, 1947 in figure 2). Later, November 26, 1947, when he was busily engaged on the thesis, his blood pressure was within the normal range, but it rose again when he was in conflict about an extra-marital love affair.

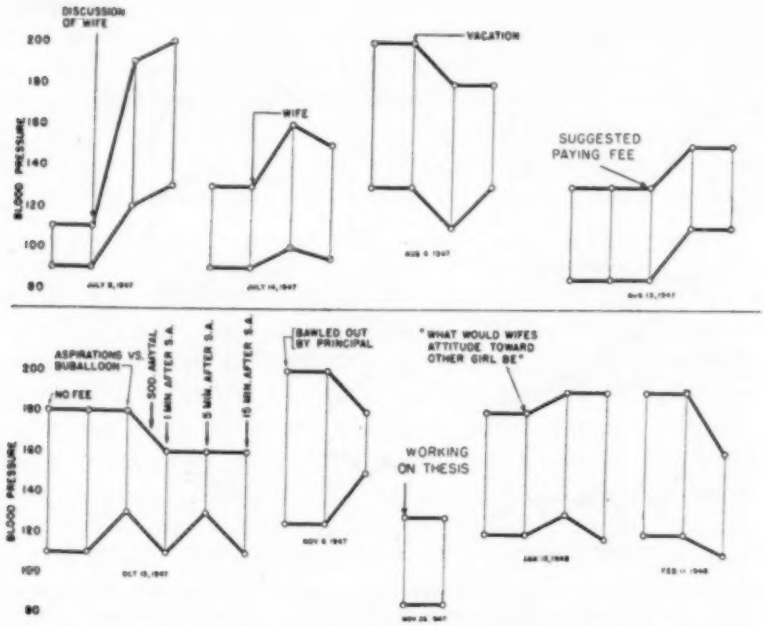

FIG. 2. Variations in level of blood pressure over one and one-half years in a 41 year old public school assistant principal. Note relatively little effect of sodium amytal administered at a time of serious fundamental conflict.

Comment: It is appreciated that inferences concerning the usual level of blood pressure cannot be drawn from single sphygmomanometric determinations even if they are made at frequent intervals, even daily, because of the rapidity with which variations occur and the fact that the person taking the blood pressure may enter into the equation. The findings do, however, support the belief that the subject's attitudes and feelings have a good deal to do with the level and that under maximally favorable circumstances the blood pressure may be within normal limits.

A 25 year old Armenian factory worker, for example, invariably had elevated blood pressure when the determination was made by his regular physician, a kindly but rather stern and quick moving individual. Even after intravenous injections of sodium amytal with strong reassurance his arterial pressure remained high as shown in figure 3. When, on the other hand, another physician whom he considered more sympathetic took the blood pressure it was repeatedly and consistently much lower (figure 3).

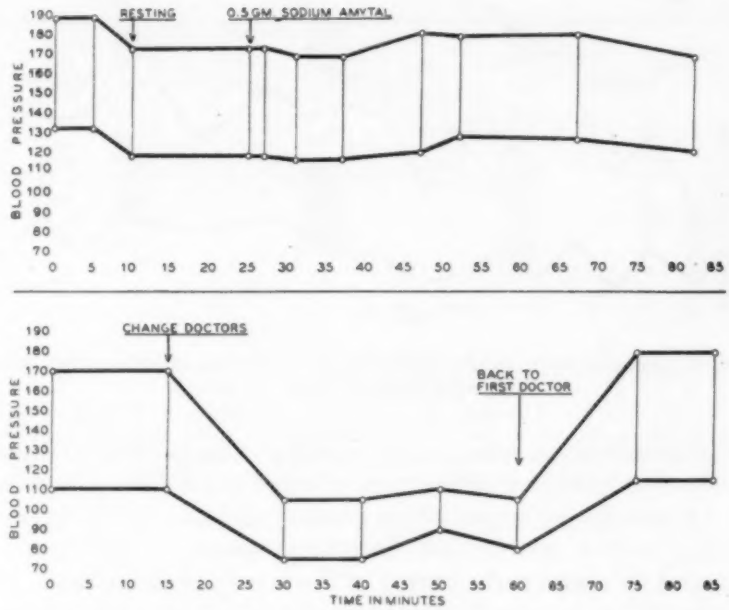

FIG. 3. Failure of intravenously administered sodium amytal to lower blood pressure while a temporary shift of physicians effected a profound lowering without drugs.

In a few subjects inferences could indeed be drawn concerning blood pressure level even from occasional determinations because there existed a 1 to 1 relationship between some symptom and elevation of blood pressure.

Thus, a 53 year old fur cutter complained of attacks of "lightheadedness" for five months prior to his first visit to the hospital. He was found to have hypertension (160 mm. Hg systolic and 100 mm. diastolic). In figure 4 are shown the variations in blood pressure recorded in this subject over a period of two years. The correlation of high readings with dizziness is clear, and hence the presence or absence of dizziness in this patient probably allows of inferences concerning the relative height of the blood pressure. His attacks were found to correlate closely with his attitudes and general feeling of security.

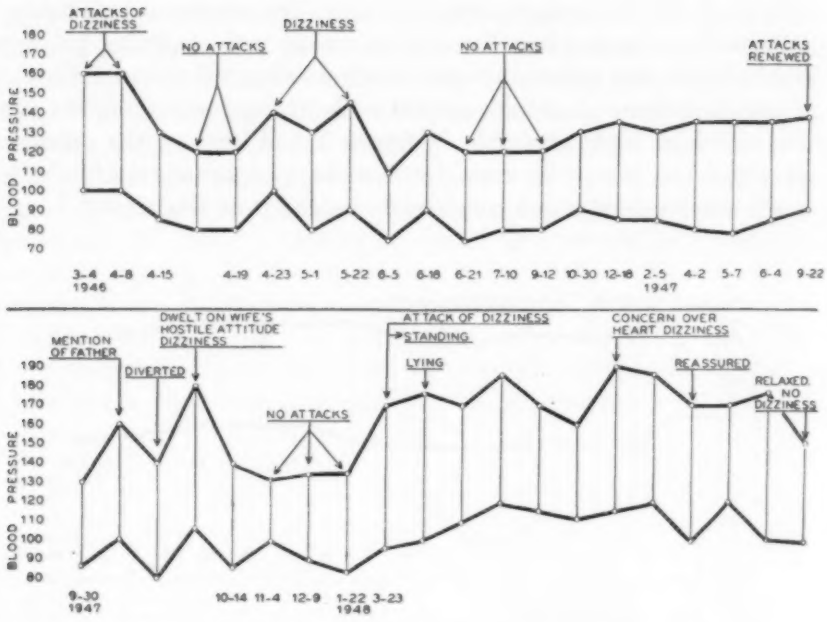

FIG. 4. Correlation of level of arterial pressure with the occurrence of attacks of "dizziness" in a 53 year old man.

B. Measurements of renal hemodynamics. Among the 21 hypertensive subjects who underwent measurement of renal blood flow it was invariably possible, by introducing topics which aroused serious conflict, to bring about a sharp rise in both systolic and diastolic pressures. These were more or less sustained throughout the period of the traumatic interview. The technical manipulations involved in the test and idle conversation, however, were not effective in raising the blood pressure.

The character of disturbance in the subjects was not one of sudden fright or alarm as in the case of Smith's subjects.[9] On the contrary, they usually appeared quiet and restrained without sweating and tremor and displayed none of the usual evidences of "nervousness." Despite their restraint and outward calm, however, they commonly asserted that they had felt anxious, frustrated or resentful during the interview. The findings in four of these subjects are shown in figure 5. They constitute a reliable sample of the whole group. It will be noted that during the control period renal blood flow was near the lower level of what is considered to be "normal." A prompt decrease in blood flow occurred coincident with the rise in arterial pressure during the interview and the diminution of renal blood flow usually outlasted the period of elevated blood pressure. The glomerular filtration rate varied only slightly but the filtration fraction rose.

When the resistance offered by the renal vasculature during the period of rise in blood pressure was determined by calculating the ratio of the mean

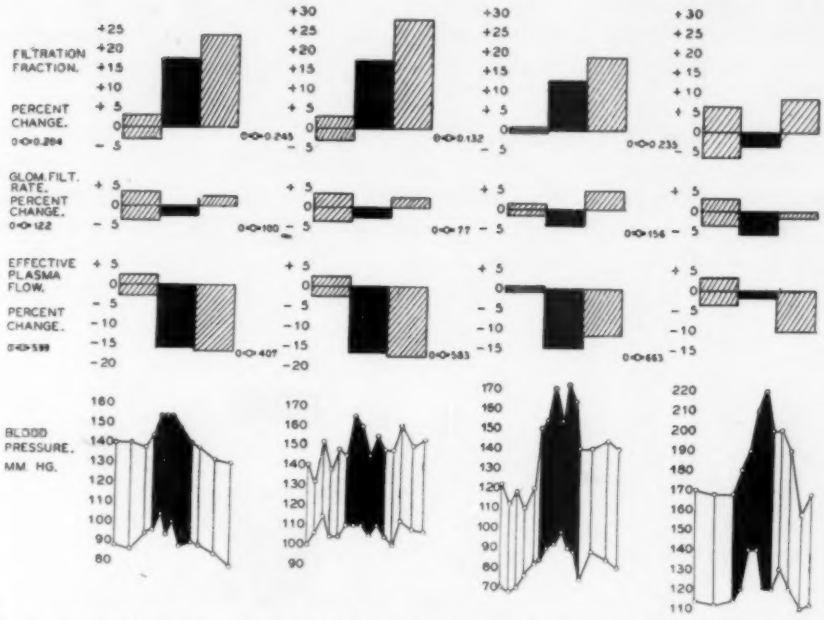

FIG. 5. Changes in blood pressure and renal hemodynamics in four representative subjects of the 21 tested.

The first section of cross-hatching represents the range of variation of three separate control periods. The mean value in each instance is shown at the left of the scale as ○=. The solid black column represents the average change during the periods of traumatic interview and the last cross-hatched column shows the average change in the post-interview periods.

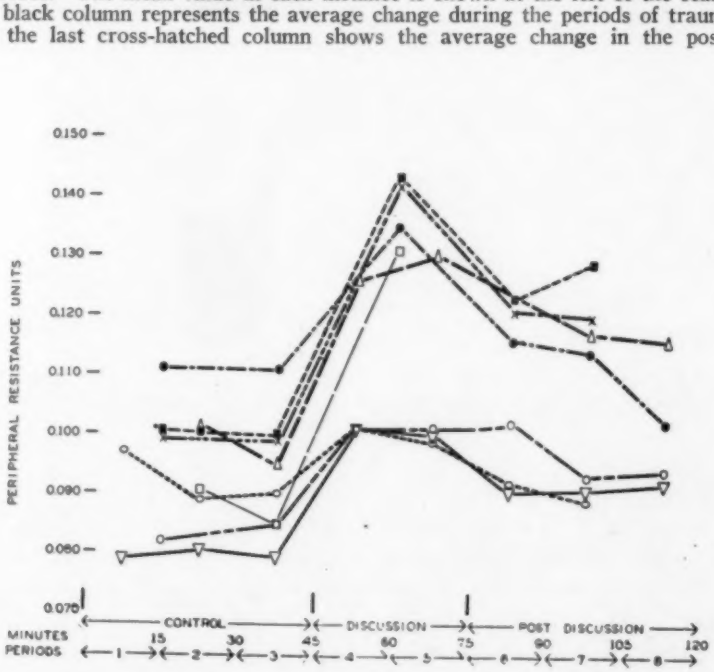

FIG. 6. Vascular resistance offered by the kidneys before, during and after interview.

blood pressure to effective renal blood flow, as high as a 45 per cent increase in resistance to blood flow was observed (figure 6). Usually the renal vasoconstrictor effects considerably outlasted the period of elevated blood pressure.

Of the normal subjects thus studied, nine displayed a moderate rise in both systolic and diastolic arterial pressures during the discussion of conflicts. With the elevation of arterial pressures there also occurred evidence of slight renal vasoconstriction. Four of the normal subjects showed no significant change in blood pressure and in the case of one subject the blood pressure decreased slightly without evidence of change in renal hemodynamics.

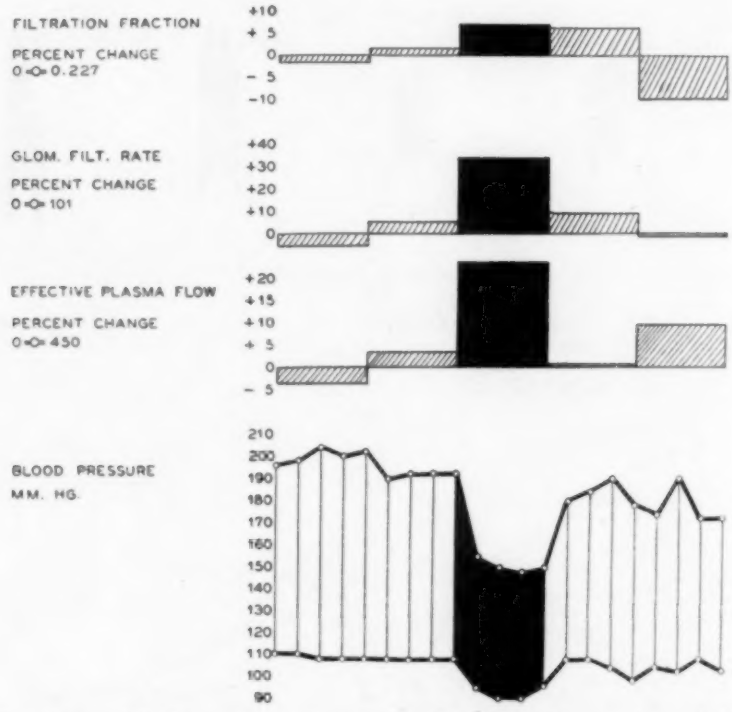

FIG. 7. Abrupt fall in arterial pressure associated with increased renal blood flow following intravenous injection of sodium amytal. Solid black column designates the values obtained during the collection period immediately after intravenous injection of sodium amytal.

In one hypertensive individual the procedure was varied in an attempt to induce a lowering of blood pressure so that its effect on renal hemodynamics could be assessed. Accordingly, a 53 year old man was given 0.5 gm. sodium amytal intravenously during a period of anxiety and relatively high arterial pressure. The injection was accompanied by strong reassurance. A considerable decrease in blood pressure was effected and with it there was observed an increase in renal blood flow and glomerular filtration. After 15

minutes of reassurance and low blood pressure, a topic of significant conflict was touched upon. Promptly the blood pressure rose to its former level and the renal blood flow and glomerular filtration rate diminished (figure 7).

Comment: Among the subjects whose renal hemodynamics were measured, the filtration fraction was always elevated when there occurred a decrease in renal blood flow. According to Smith [19] this indicated an increase in the efferent arteriolar resistance. The application of the formulae of Lamport,[20-23] however, yielded evidence of a constriction of afferent arterioles as well.

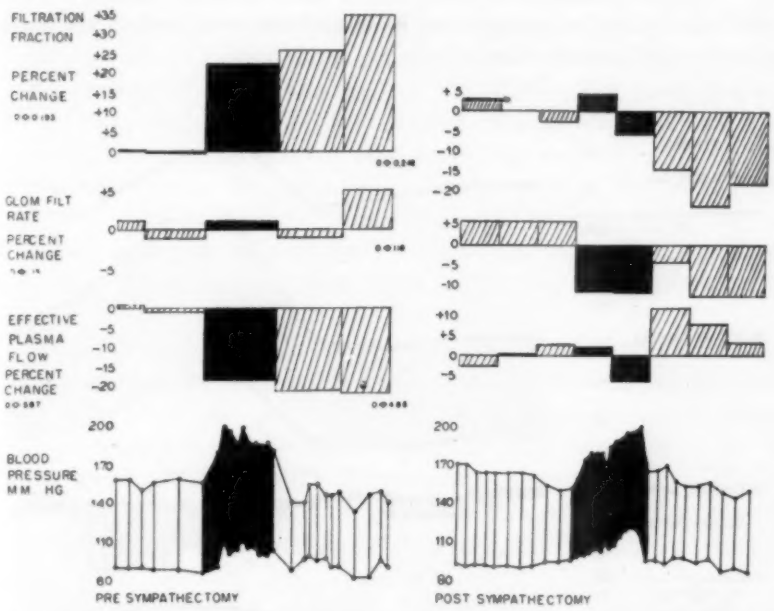

FIG. 8. Modifiability of blood pressure and renal hemodynamics by traumatic interview pre- and post-sympathectomy (Smithwich thoraco-lumbar procedure).

Because epinephrin also induces a fall in plasma flow and rise in filtration fraction, it has been proposed that the efferent arteriole was subject to the control of the adreno-sympathetic system. In favor of this inference is the observation of Richards and Plant [24] and Winton [25] of expansion of the kidney with fall in renal blood flow noted during direct observation of the kidney following minute doses of epinephrin. Livingston observed the same effect after weak stimulation of the splanchnics.[26] Against this interpretation is the fact that sympathectomy and high spinal anesthesia in humans fail to cause significant changes in renal blood flow [16, 27, 28, 29, 30] and similar observations in the case of the autotransplanted kidney in the dog.[31] It is conceivable that since all these studies were done in the basal or "standard" state the failure to observe changes in renal blood flow might be attributable

to relatively minimal sympathetic activity during periods of rest. Therefore, special note of these relationships was made in the six hypertensive subjects who were restudied in the experimental interview situation at varying intervals following sympathectomy.

C. Effects of sympathectomy. The prototype of the results observed among the six sympathectomized subjects is shown in figure 8 where the pre-sympathectomy findings are contrasted with those post-sympathectomy. It is evident that although after sympathectomy the blood pressure rose during the traumatic interview just as readily as it did before, the accompanying renal vasoconstriction no longer occurred and there was no rise in filtration fraction. The peripheral resistance in the kidney as calculated by the ratio mentioned above no longer rose so high and the component attributable to efferent arteriolar constriction was lost.

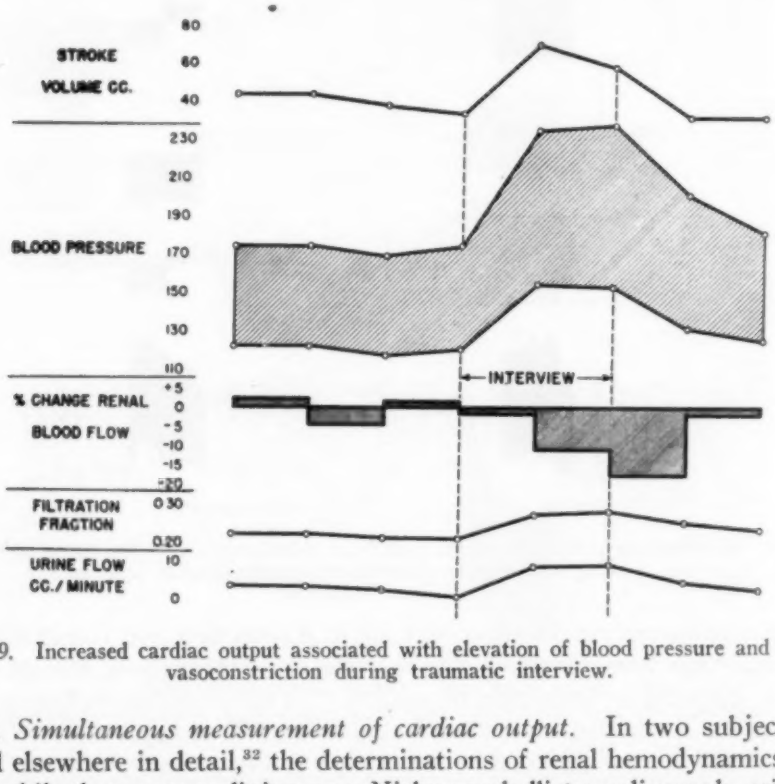

FIG. 9. Increased cardiac output associated with elevation of blood pressure and renal vasoconstriction during traumatic interview.

D. Simultaneous measurement of cardiac output. In two subjects, reported elsewhere in detail,[32] the determinations of renal hemodynamics were made while they were reclining on a Nickerson ballistocardiograph, critically damped and connected to a direct writing recorder.[33] In both instances during the traumatic interview the blood pressure rose briskly and at the same time there was recorded a significant increase in stroke volume as well as heart rate and hence in cardiac output (figure 9).

One of these subjects was retested in this fashion after sympathectomy. During the interview her cardiac output increased as it had before operation

and the renal findings were similar to those of our other sympathectomized subjects described above.

Comment: The inferences which can be drawn from these data are: (1) It is possible at will to invoke in hypertensive subjects an accentuation of their characteristic biologic pattern of mobilization by confronting them with an adequate threat to their security. (2) This reaction includes a sharply decreased supply of blood to the kidneys. The blood flow is obviously shunted elsewhere since the cardiac output may be increased and the pressure in the system is higher. (3) The renal vasoconstriction involves both the afferent and efferent arterioles. (4) This process may be temporarily reversed by appropriate measures which lower the blood pressure. (5) After bilateral lumbodorsal sympathectomy the general mobilization response in reaction to threats is modified but not abolished. It is still possible to elevate the blood pressure but the shunting of blood from the renal bed to such a degree no longer occurs. The renal vasoconstrictor effect which is lost after sympathectomy is predominantly that involving the efferent arteriole. The afferent arteriole may be governed by an intrinsic or humoral mechanism. These data reinforce the conclusions of Ferris referred to earlier, in which he identified a persistent humoral factor which induced elevation of blood pressure in response to situational threats following the elimination of neural effects.

Concerning the pathogenesis of this mobilization response, the older concepts of sympathicotonia and organ inferiority are inadequate because among hypertensives the blood pressure does not necessarily rise in response to stress. Under appropriate circumstances it may even fall. The direction of change appeared to depend rather on what the particular stimulus meant to the subject. When a reaction of mobilization was not evoked and the subject on the other hand felt defeated or overwhelmed a depressor reaction occurred.

E. Nature of pressor stimulus—variability of cold pressor effect. A striking example of this phenomenon reported in detail by Stevenson and Duncan [32] was encountered when a cold pressor test was administered to a pregnant hypertensive at a time when she was hyperreactive to noxious stimuli of all sorts, felt overwhelmed and unable to bear the pain involved. Accompanying the pain she experienced nausea, sweating and the blood pressure fell abruptly. A few minutes earlier a brisk pressor response had been elicited by a discussion of her forthcoming delivery, an event which to her was fraught with mixed feelings of guilt, frustration and resentment (figure 10).

Examples of variability in the degree and type of cold pressor response were frequently encountered. Again the significance of the event appeared to influence its effect upon arterial pressure. For example, when one man, a 28 year old steam fitter, thought that the decision as to whether or not he would undergo a mutilating sympathectomy hinged upon the outcome of a

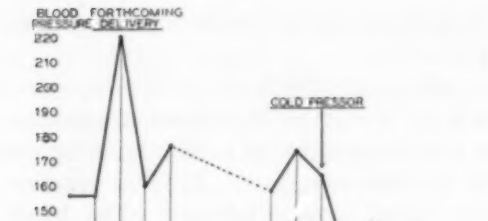

FIG. 10. Brisk rise in blood pressure in a hypertensive subject associated with conflict and resentment during discussion of forthcoming parturition. Precipitate fall when hand was plunged into ice water in a period of dejection, exhaustion and feelings of being overwhelmed.

cold pressor test, he displayed the response of a "hyperreactor." Later the same day, when he was reassured that the operation was not considered necessary, his blood pressure was lower initially and the test produced a "hyporeactive" response. Even at times when his initial pressure was high, however, his response was "hyporeactive" when the performance of the test had no special significance for him (figure 11).

The phenomenon of hypertensive reactions under one set of circumstances and hypotensive under another has also been recognized during the day-to-day follow-up of the clinical course of patients. This is exemplified by the

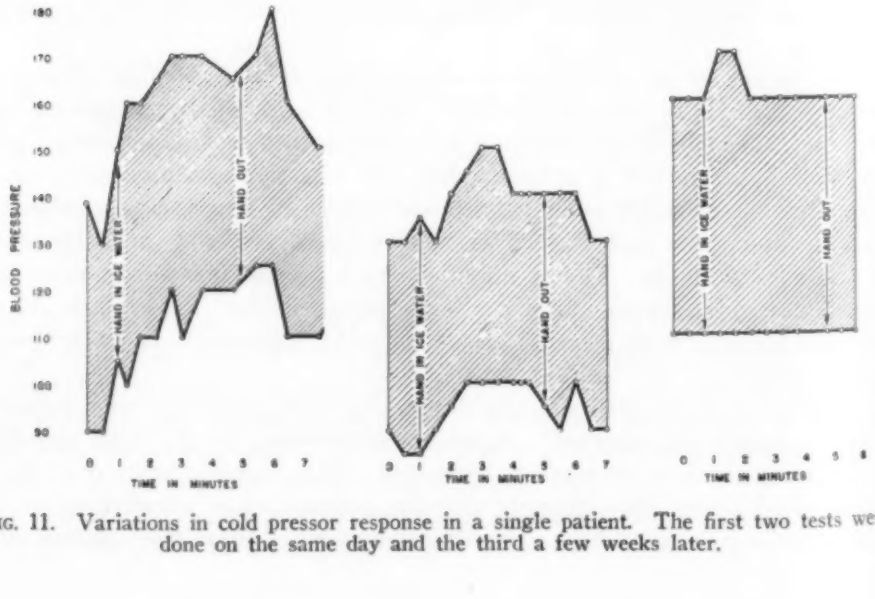

FIG. 11. Variations in cold pressor response in a single patient. The first two tests were done on the same day and the third a few weeks later.

case of a 48 year old married Jewess whose chief conflicts concerned the unsalutary relationship between her husband and older son. The former had not wanted children and considered the patient's open adulation for and extremely protective attitude toward their son a direct threat to his security. Consequently he punished the boy at every opportunity. The patient's hypertension was discovered at the time when her son was drafted into the Army. It persisted during the subsequent period until the news came that the boy was to be sent overseas. She felt overwhelmed and defeated by this prospect and continued dejected with much lower blood pressure until her resentment was again aroused by conflict between her husband and son and with that her blood pressure rose again to hypertensive levels. Later, at a time when the patient was catheterized, a procedure to which she reacted with overwhelming shame, she again displayed a precipitous transitory fall in blood pressure with sweating and tachycardia (figure 12). This observation has been repeated on three separate occasions with similar results each time.

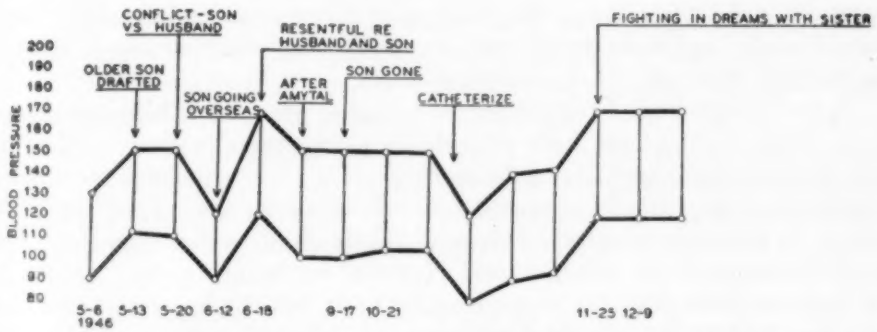

FIG. 12. Episodes of lowered blood pressure associated with feelings of defeat in response to overwhelming events occurring in a subject with essential hypertension who reacted to most stresses with more aggressive feelings and elevation of blood pressure.

Comment: Wolf and Wolff [34] and more recently Hickam, Cargill and Golden [35] have similarly shown that elevation of blood pressure constitutes a part of only one kind of cardiovascular response to situational threats, a hyperdynamic one. Under appropriate circumstances another subject or even the same individual may react with a hypodynamic response including a lowering of blood pressure. The latter was characteristically accompanied by feelings of defeat or dejection in contrast to the tense, aggressive attitude which accompanied hypertension.

F. Personality features and reactions of persons with arterial hypertension. Our personality study and diary of attitudes and behavior of these subjects substantiated in a striking way the concept that their hypertension represented an emergency mobilization pattern inappropriately used and unduly sustained. Fifty cases out of 58 on careful study generally fitted the following description. In agreement with the findings of Sheldon [36] they

were more square and muscular than average. They were non-reflective and displayed a taste for dealing with problems by action. Many of them exhibited signs and symptoms of excessive skeletal muscle tension. From the standpoint of attitudes as well as circulatory physiology they were mobilized for combat, but did not engage in it against the pertinent adversary. Under a façade which was often affable and easy going, they were tense, wary and suspicious, afraid of committing themselves. They were poised to strike, but withheld their punch with a guilty fear of its consequences. At the same time they displayed a strong need to conform and keep peace. This, coupled with inability to throw themselves wholeheartedly into things because of fear and suspicion, made it difficult for them to believe strongly in anything or to derive real satisfaction from their accomplishments. They felt a need to show prowess without exhibiting aggression and continually feared that they would not succeed in doing so.

Hypertensive individuals were found to take out their aggression in some vicarious way, by excelling in sports, or merely by an excess of general activity or excessive eating. They were prominently preoccupied with appearances and saving face. As children they were all unduly shy. They blushed easily and were rarely able to admit they were wrong. Most of the married ones selected domineering mates.

In the background of the subjects we studied were the following common circumstances which may have provided conditioning situations. Many of their mothers were stiff and domineering. They were inclined to demand compliance and withheld approval for failure to do so. They especially refused to tolerate outbursts of anger. Their children felt that they were forced to compete for affection and approval by being "good." Many of our hypertensives dealt fairly successfully with this challenge and managed for a time, at least, to consider him- or herself "closest" to the mother. This accomplishment inevitably involved the development of strong hostility toward the mother which was suppressed with varying degrees of success but was associated with guilt.

In brief, our hypertensive subjects, often gentle, poised and apparently easy going, were filled with aggressive drive which was tightly restrained by a need to please.

In order to bring into focus the characteristics of the hypertensive reaction pattern we compared them with a group of 150 subjects suffering from chronic vasomotor rhinitis or bronchial asthma reported in detail elsewhere.[37, 38] These latter in general were of a more linear build, less square and muscular and less hearty. They were found to display predominantly attitudes and behavior of defense and non-participation in contrast to the offensive aggressive but thoroughly bridled striving of the hypertensive. They were less preoccupied with pleasing but their attempt was to shut out rather than deal with the noxious environment.

Striking confirmation of this formulation of the general character structure and attitudes of the hypertensive implying his proclivity for meeting

challenges with a pattern of tightly reined mobilization is found in Friedman and Kasanin's study of apparently identical twins, one of whom was hypertensive.[39] They found that the non-hypertensive twin was the brighter and stronger of the two and the better in school. He was more relaxed and satisfied, expressed anger easily and recovered rapidly from humiliations. The hypertensive twin felt that he was at a competitive disadvantage with his brother, spent a great deal of time and energy trying to please people and had no enemies but suppressed resentment and hostility and carried them within him for a long time. He worked extremely hard and was "successful" but never felt much satisfaction in his day-to-day living.

Similar reaction patterns among hypertensives have been described by Binger and his associates,[4] by Alexander [2] and Saul.[3]

In several subjects an episode of lowered arterial tension followed a fairly uninhibited physical expression of aggression.

In figure 13 is illustrated an occurrence in a 36 year old purveyor of illicit merchandise who was able to cope with many "tight spots" but not with the contemptuous attitude toward the subject held by his brother-in-law with whom he was forced to live. After a particularly humiliating episode he came to the laboratory with a blood pressure of 165 mm. Hg systolic and 110 mm. diastolic. The results of his repressive pattern were pointed out and he was encouraged to deal with the problem another way. He went out and returned after "beating up" his brother-in-law. At that time his blood pressure was 125/85. He said that he felt relaxed and vindicated (figure 13).

To test further the relevance of situation to blood pressure our subjects were followed from week to week over a period of several years. They were

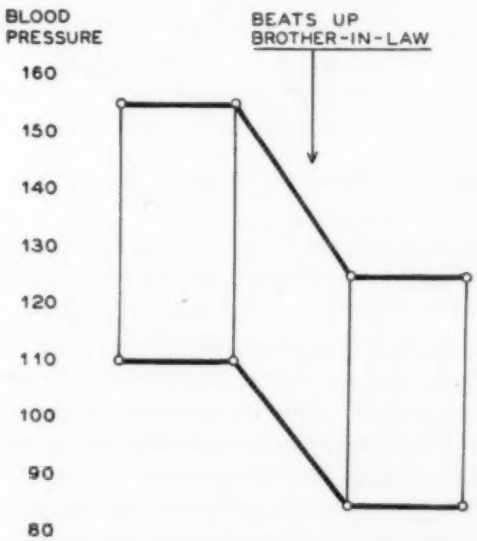

FIG. 13. Reduction of arterial pressure in an hypertensive subject following a fairly uninhibited physical expression of aggression.

given reassurance, encouragement, advice with their problems and opportunities to express their feeling and to discuss their interpersonal conflicts. An example of improvement under such management is provided by the case of a 28 year old steamfitter illustrated in figure 14. His principal conflicts related to his father who had forced him into the steamfitting business shortly before he deserted his wife and children. The patient, who really wanted to be a half time artist and half time prize fighter, was encouraged to sell his steamfitting tools. Following this his blood pressure remained relatively

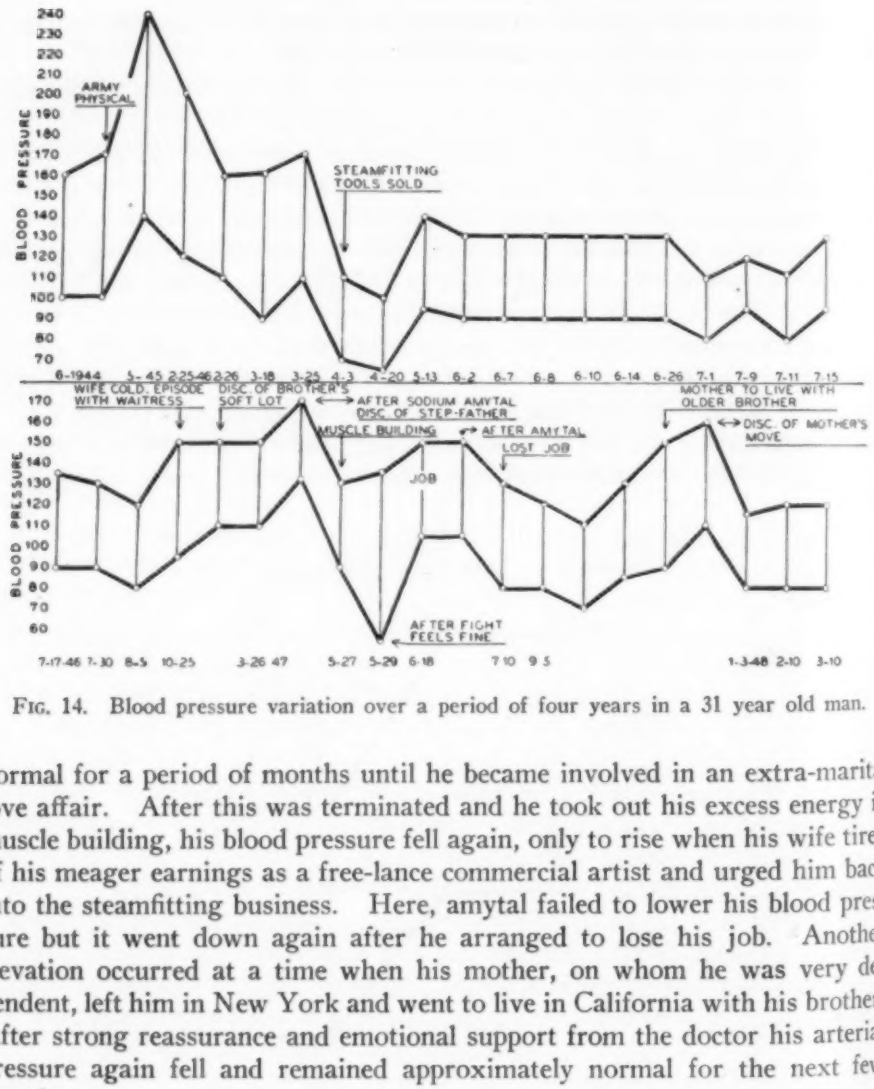
BLOOD PRESSURE
ARMY PHYSICAL
STEAMFITTING TOOLS SOLD
6-1944 5-45 2-25-46 2-26 3-18 3-25 4-3 4-20 5-13 6-2 6-7 6-8 6-10 6-14 6-26 7-1 7-9 7-11 7-15
WIFE COLD, EPISODE WITH WAITRESS
DISC. OF BROTHER'S SOFT LOT
AFTER SODIUM AMYTAL
DISC. OF STEP-FATHER
MUSCLE BUILDING
AFTER AMYTAL
LOST JOB
JOB
MOTHER TO LIVE WITH OLDER BROTHER
DISC. OF MOTHER'S MOVE
AFTER FIGHT FEELS FINE
7-17-46 7-30 8-5 10-25 3-26 47 5-27 5-29 6-18 7 10 9 5 1-3-48 2-10 3-10

FIG. 14. Blood pressure variation over a period of four years in a 31 year old man.

normal for a period of months until he became involved in an extra-marital love affair. After this was terminated and he took out his excess energy in muscle building, his blood pressure fell again, only to rise when his wife tired of his meager earnings as a free-lance commercial artist and urged him back into the steamfitting business. Here, amytal failed to lower his blood pressure but it went down again after he arranged to lose his job. Another elevation occurred at a time when his mother, on whom he was very dependent, left him in New York and went to live in California with his brother. After strong reassurance and emotional support from the doctor his arterial pressure again fell and remained approximately normal for the next few months.

Discussion

The concept of bodily economy being maintained by an equilibrium of opposing forces acting on organs and organ systems commands wide interest and sympathy at present. It is also clear that the mass-action equations which are responsible for maintaining these equilibria are so highly sensitive that the reaction is caused to go predominantly in one or another direction by changes so minor that they cannot be detected by current sensitive methods of measurement.

Whether adaptive measures are automatic or voluntary is apparently unimportant as far as their relevance to the homeostatic mechanism is concerned. For example, the automatic thermoregulatory mechanisms such as increased muscle tension, shivering, or sweating are of the same order of phenomena as the voluntary ones, such as walking rapidly or putting on long underwear when the day is cold. They are all aimed at maintaining the homeostatic balance between heat production and heat loss.

The ducking which occurs when a missile is thrown at one's head may be automatic or voluntary but the distinction is unimportant. It is an appropriate defensive gesture to anticipate and ward off the adverse weighting of the equation which maintains homeostasis.

The tense, alert posture of sitting on the edge of the seat with which one anticipates a motorcar accident is a similar protective gesture but is far less appropriate. It would appear to have significance atavistically as a "readiness to spring," appropriate when dealing with danger which can be sidestepped or run away from but inappropriate and potentially costly when invoked in a motor car. A more satisfactory posture to assume in anticipation of an auto accident would be to relax completely and curl up on the floor of the car. By the same token elevation of blood pressure is an inappropriate way to meet the hazards of sibling rivalry or problems of marital adjustment. The difficulty would appear to consist in reserving the biologic pattern of mobilization for short term emergencies in which it is appropriate or at least not harmful, instead of adopting it as a way of life and applying it inappropriately to long standing threats from conflicts of interpersonal relations in job or family. Perhaps hypertension is an ancient protective reaction to preserve homeostasis, potentially useful to Man, especially in his early days, but certainly most costly and inappropriate when adopted as a sustained long term adaptive pattern.

Support for the point of view that such a pattern of reaction involves the cerebral cortex as well as lower neural structures derives from the work of Pool and his associates [42] who performed bilateral topectomy on two psychotic subjects with essential hypertension, removing the medial portion of Brodman areas 9 and 10. Prior to operation the blood pressure of the first subject ranged between 200 to 220 systolic and 120 to 130 diastolic. For two years since operation the average range has been 170 to 180 systolic and 100 diastolic. The continued moderate hypertension in this subject

suggests that part of the hypertensive mechanism at least may become irreversible to the interruption of cortical pathways. The second subject has only been followed for five months postoperatively but coincident with clinical improvement characterized by lessening of depression and decreased preoccupation with problems and conflicts, the blood pressure fell from an average range of 180 to 200 systolic and 110 to 120 diastolic to 120/80.

It has already been pointed out that the hypertensive subject differs in general from subjects with asthma in body build, personality structure, attitudes and behavior. Why a man, when his security system is seriously threatened, should develop hypertension instead of asthma, peptic ulcer or colitis, cannot be stated but it would appear that these disorders represent various possible patterns of reaction to threats. When a man's face is slapped by an adversary's glove he may choose pistols, sabres or boxing gloves, or he may elect to run away, to collapse at the feet of his challenger or sidestep the incident by retracting or making a joke of the incident. Why he chooses one course rather than another depends upon a myriad of factors including his inherited tendencies, his early experiences, his cultural background, his habits and skills, etc. The significant question for present consideration is the character of pattern which he does select and what its implications are for his health and survival. Hypertension is a costly protective device when utilized for more than short term emergencies. Adopted as a way of life it may lead to irreversible cardiovascular and renal damage and eventual death of the organism.

Summary and Conclusion

1. A group of 58 subjects with essential hypertension has been studied from the standpoint of overall reactivity to threats arising out of problems of day-to-day living.

2. It was found that they meet these threats and challenges with an attitude of restrained aggression and display a vascular reaction characterized by elevation in blood pressure and renal vasoconstriction.

3. Both the afferent and efferent glomerular arterioles participate in the constriction.

4. Following thoraco-lumbar sympathectomy the renal blood flow when the subject is at rest is unchanged. The arterial pressure continues to show elevation in response to situational threats, but the efferent glomerular arteriolar constriction during such rises is abolished. The constriction of the afferent arterioles persists.

5. The general attitudes, reaction patterns and behavior of hypertensives differ from those of subjects with bronchial asthma. In general the former are more offensive and the latter more nearly defensive in their dealings with life.

6. Hypertension may represent an atavistic protective reaction of mobilization, invoked inappropriately by these subjects to deal with day-to-

day stresses and threats arising out of problems of interpersonal relation. It becomes harmful and leads to illness when this essentially emergency pattern is adopted as a way of life.

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AUREOMYCIN—A NEW ANTIBIOTIC: EVALUATION OF ITS EFFECTS IN TYPHOID FEVER, SEVERE SALMONELLA INFECTIONS AND IN A CASE OF COLON BACILLUS BACTEREMIA *

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There has been a notable lack of success in the treatment of typhoid fever and salmonella infections with the chemotherapeutic and antibiotic agents that are now available. This has been true even with streptomycin which is usually quite effective against the causative organisms in vitro. Moreover, the failures of streptomycin in these infections and in some others like brucellosis have not usually been associated with the appearance of highly resistant variants as they are in most other infections, nor have they generally been associated with the presence of large and inaccessible areas of suppuration. Because these infections may be quite variable in their clinical course, it may be difficult to evaluate the effectiveness of any given agent without careful study of its use in cases of varying severity.

In this paper are presented the results of clinical and bacteriologic observations in a few cases of typhoid fever and salmonella infections and in a case of colon bacillus bacteremia that have been treated with a new antibiotic, aureomycin. Tests with this antibiotic in vitro and some observations in experimental infections in animals have suggested that this agent was effective against a large variety of gram-positive and gram-negative organisms including those of the typhoid-salmonella group and that it was also effective against infections with rickettsias and with viruses of the psittacosis-lymphogranuloma venereum group. This antibiotic therefore seemed worthy of a clinical trial to determine its field of usefulness in the treatment of human infections. A brief summary of the results of its use in 100 cases of various bacterial infections has been presented elsewhere.[1] Because of their special interest, the findings in the present cases are reported here in somewhat greater detail.

Some of the details concerning the isolation of aureomycin, its pharmacologic properties and its activity against various bacteria in vitro and against experimental infections in animals with a variety of different bacteria, rickettsias and viruses have been presented by workers of the Lederle Laboratories Division, American Cyanamid

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Company at a Conference on Aureomycin sponsored by the New York Academy of Sciences, July 21, 1948. Reports of other laboratory investigations with this agent and of its clinical use were also made at this conference by several other groups of workers including the present authors.

Aureomycin was found to be highly stable in the form of a dry powder, and it also maintained its potency for at least two weeks when kept at high concentrations in distilled water at pH 4.0, either at incubator or ice box temperatures. It loses potency very rapidly, however, when kept at low concentrations in broth, serum or blood agar at 37° C. and somewhat less rapidly at 4° C.[2]

Bacteriologic observations in this laboratory [2] have indicated that aureomycin is active in vitro against many recently isolated pathogenic strains of bacteria including various cocci and gram-negative bacilli and also against penicillin resistant, streptomycin resistant and streptomycin dependent organisms. The number of organisms inoculated and the pH of media greatly influence the antibacterial action of aureomycin and it is effective only against actively multiplying organisms. There is no marked tendency for organisms to become resistant to aureomycin after single or repeated exposures of large numbers of bacteria or during treatment of patients with this agent. A moderate increase in resistance, however, was attained in some strains by repeated subculture in the presence of increasing concentrations of the antibiotic.

In human subjects aureomycin activity appears quite rapidly in the urine after its oral administration, and concentrations of 64 to 256 μ g. per ml. may be demonstrated in urine collected between two and 16 hours after a single dose of 0.5 or 0.75 gram in adults. The greatest rate of excretion after such doses occurs between two and eight hours. Some aureomycin activity could still be demonstrated in the urine for as long as 72 hours after a single dose or after the last of a series of oral doses. The maximum values for plasma concentrations of aureomycin after single or multiple oral doses of 0.5 or 1.0 gram were usually found to be about 2 μ g. per ml. or less but the methods used for these determinations were not entirely satisfactory.[3, 4]

Clinically aureomycin appears to be effective when given by mouth and is relatively nontoxic.[1] Intramuscular doses of the hydrochloride dissolved in distilled water are very irritating due to the high acidity of the substance but the irritation may be overcome somewhat by the use of proper buffers and/or by the incorporation of procaine with each injection. Favorable results were reported, at the conference mentioned, in early clinical trials in cases of lymphogranuloma venereum,[5, 6] granuloma inguinale,[5] various types of infections of the eye,[7] gonorrhea,[1] pneumonia,[8] meningococcemia,[8] nonspecific urethritis,[1] brucellosis,[9] typhoid fever [1] and some urinary tract infections.[1, 4, 9] The results in the treatment of various rickettsial infections [1, 10] were most encouraging.

Patients, Materials and Methods

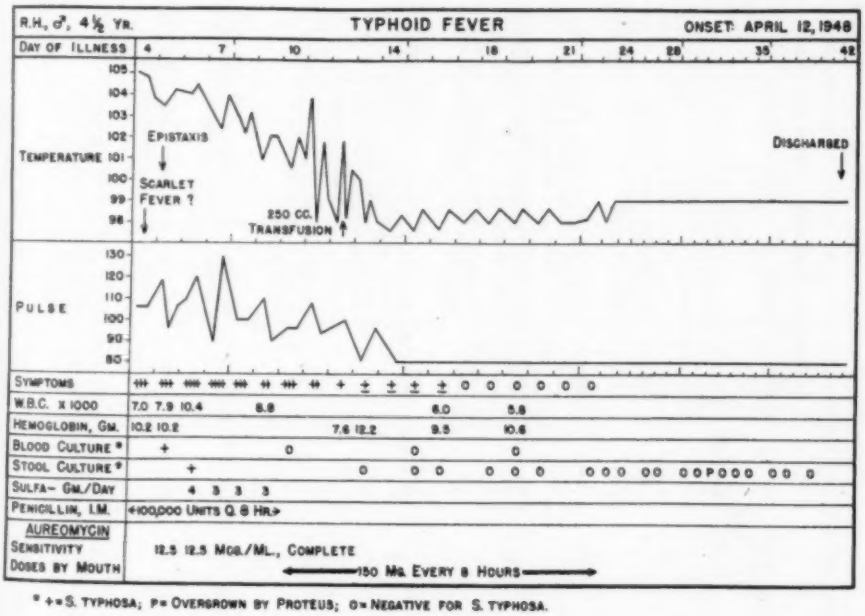
The patients selected for this study were admitted to the Boston City Hospital in the spring of 1948. They varied in age from 14 months to 80 years. Except for the typhoid carrier, they were all acutely ill and the causative organism was obtained from their blood and/or stools before treatment was begun. All of the aureomycin was given by mouth except in two patients who received small doses intramuscularly in addition. Since these patients were among the first to receive oral therapy and the toxicity of the compound in humans was not known, the doses used at first were considerably smaller than those which subsequent experience has shown to be feasible and perhaps necessary.

Specimens of blood, stools and urine were obtained before, during and after treatment with aureomycin whenever indicated and feasible. The isolation and identification of the organisms were carried out by Marion E. Lamb and A. Kathleen

Daly in the Bacteriology Laboratory of the Mallory Institute of Pathology. Tests for sensitivity to aureomycin were carried out chiefly by a surface streak method on agar plates containing varying concentrations of the antibiotic.[2] The concentrations of aureomycin in blood and urine were determined by a serial dilution method[3]; the organism employed in most of these tests was the streptococcus 98, but another organism bacillus No. 5 obtained from Dr. B. M. Duggar was used later. These tests were carried out with the technical assistance of Paul F. Frank, Clare Wilcox and Janice M. Bryan. Details of methods used are given elsewhere.[2, 3]

Case Reports

The significant clinical and bacteriologic data in the various patients are shown in figures 1 to 9 and in table 1. Only a few brief comments will be made concerning the features of special interest in each of these patients. The case of the typhoid carrier is of particular interest and will be considered separately.



* + = S. TYPHOSA; P = OVERGROWN BY PROTEUS; 0 = NEGATIVE FOR S. TYPHOSA.

FIG. 1.

Typhoid Fever. Five of the patients were treated for typhoid fever. The first of these patients, R. H. (figure 1), was first seen at the South Department on the tenth day of illness after he had apparently failed to respond to treatment with penicillin and sulfadiazine, although his temperature and pulse rate appeared to be on the down grade at the time. Clinical improvement in this patient was quite rapid after aureomycin treatment was started and typhoid organisms could not be obtained from cultures of his blood or stools thereafter, although they had previously been obtained on one occasion

TABLE I

Summary of Relevant Clinical and Laboratory Findings in Cases of Typhoid Fever, Salmonella Infections and Colon Bacillus Bacteremia Treated with Aureomycin

Patient	Sex	Age, Yrs.	Diagnosis, Organism	Sensitivity, Complete μg./ml.	Clinical Findings before Aureomycin Therapy					Aureomycin Therapy			
					Severity	Fever	Symptoms	Previous Chemotherapy		Day of Disease		Dosage (oral, except when noted)	Total, Gm.
								Drug	Days	Begun	Ended		
R. H.	M	4½	Typhoid fever, *S. typhosa*	12.5	+++	105–102	Disoriented, vomiting, distended, diarrhea. Hemoglobin 10 gm.	Sulfaguanidine Sulfadiazine Penicillin	1 4 7	10	23	0.15 gm. every 8 hrs.	5.85
J. H. (sister of R. H.)	F	1½	Typhoid fever, *S. typhosa*	12.5	++	104–101	Vomiting and apathy. Had typhoid vaccine 2 days before onset	None		8	23	0.05 gm. every 8 hrs.; then every 6 hrs.	3.0
L. O'C.	F	2	Typhoid fever, *S. typhosa*	12.5	+++	100–105	Irritable, vomiting, diarrhea, anorexia	Penicillin	5	8	21	0.15 and 0.1 gm. alternately every 12 hrs.	3.4
M. O'C. (sister of L. O'C.)	F	3	Typhoid fever, *S. typhosa*	25	++	103	Anorexia, listless, diarrhea, distended. Hemoglobin 75%	None		5	26	0.1 gm. every 6 hrs.	8.4
A. L.	M	60	Typhoid fever, *S. typhosa*	6.3	++++	101–102.4	Remission of fever 12 to 18 days after onset, then acutely ill with headache, diarrhea, sweating and prostration. Hemoglobin 9 gm.	None		22	44	0.5 gm. every 12 hrs. for 3 days; every 8 hrs. for 6 days; then every 6 hrs.	38.5
M. E.	F	73	Chronic carrier, *S. typhosa*	12.5	0	0	Asymptomatic, probably source of fatal cases in a nursing home	None		1 yr.	+31	0.25 gm. every 8 hrs.; 2 months later—4 doses of 1.0 gm.; then 0.5 gm. every 6 hrs.	23.0 20.0
P. E.	F	26	Enteritis, *S. newport*	25	+++	101–103	Malaise, prostration, abdominal cramps, diarrhea, nausea, vomiting	Penicillin	3	12	20	0.25 gm. every 6 hrs. for 1 day; then every 12 hrs.	5.25
C. M.	F	51	Enteritis, *S. newport*	6.3	++++	101	In "shock," dehydrated, severe diarrhea, vomiting and distention	Penicillin	3	12	15	0.5 gm. every 6 hrs. + 20 mg., intramuscularly, every 12 hrs.	7.0 +0.14 i.m.
A. A.	M	68	Bacteremia; osteomyelitis of spine; psoas abscesses, *S. cholerae suis*	6.3	+++	102–104	Back pain, chills, urinary frequency, incontinence, abdominal distress, cough and disorientation	Penicillin	3	+4‡	+15	0.5 gm. every 6 hrs. + 20 mg., intramuscularly, every 12 hrs.	21.0 +0.44, i.m.
F. S.	F	80	Bacteremia, source undetermined, *E. coli communis*	12.5	++++	102 (irregular)	Anorexia, epigastric pain, weight loss, constipation, jaundice, hepatomegaly, epigastric mass	Penicillin	11	?	+15	0.25 gm. every 4 hrs.; then 0.75 gm. every 8 hrs. last 4 days	22.5

TABLE I—*Continued*

Patient	Bacteriologic Findings*				Clinical Effects								Estimation
	Specimen	Day of Disease	Aureomycin Concentration, μg./ml.		Fever		Symptoms		Blood Count		Urine		
			Serum	Urine	Day of Disease	Hours after Aureomycin	Day of Disease	Hours after Aureomycin	Day of Disease	Hours after Aureomycin	Day of Disease	Hours after Aureomycin	
R. H.	Blood	10	0.78	1,000	10	2	10	2	10	2	10	2	Cure
J. H. (sister of R. H.)	Blood	8	0.78	1,000	8	2	8	2	8	2	8	2	Cure
L. O'C.	Blood	8	0.78	1,000	8	2	8	2	8	2	8	2	Cure
M. O'C. (sister of L. O'C.)	Blood	5	0.78	1,000	5	2	5	2	5	2	5	2	Cure
A. L.	Blood	22	0.78	1,000	22	2	22	2	22	2	22	2	Cure
M. E.	Stool	1 yr.	0.78	1,000	1 yr.	2	1 yr.	2	1 yr.	2	1 yr.	2	Cure
P. E.	Blood	12	0.78	1,000	12	2	12	2	12	2	12	2	Cure
C. M.	Blood	12	0.78	1,000	12	2	12	2	12	2	12	2	Cure
A. A.	Blood	+4‡	0.78	1,000	+4‡	2	+4‡	2	+4‡	2	+4‡	2	Cure
F. S.	Blood	?	0.78	1,000	?	2	?	2	?	2	?	2	Cure

F. S.	F	80	Bacteremia, source undetermined, *E. coli communis*	12.3	+ + + +	102 (irregular)	Abdominal epigastric pain, weight loss, constipation, jaundice, hepatomegaly, epigastric mass					then 0.75 gm. every 8 hrs. last 4 days	

TABLE 1—*Continued*

Patient	Bacteriologic Findings*				Clinical Effects				Toxic Effects	Estimation of Effect of Aureomycin
	Source	Relation to Therapy			Days from 1st Dose Until:			Effect on Symptoms; Other Therapy		
		Before	During	After	Afebrile	Improved	Well			
R. H.	Blood Stool	+ +	0 0	0 0	3	1	8	Distention persisted after general improvement. Transfused on day 12	None	Good
J. H.	Blood Stool	+ +	— + 1 day, then 0	— 0	7	4	8	Vomiting stopped, appetite good and looked brighter after fourth day	Vomited 4 days	Doubtful
L. O'C.	Blood Urine Stool	+ 0 0	+ 1 day, then 0 0 0	— — —	5	5	6	Fever declined gradually after aureomycin begun, but improved only after 5 days	None	Good?
M. O'C.	Blood Urine Stool	+ 0 0	0 0 0	— 0 —	20	8	20	Got worse, T 105, for 3 days; diarrhea stopped eighth day; gradually improved. Transfused on days 8 and 9	Vomited early doses†	None
A. L.	Blood Urine Stool	+ 0 +	+ 6 days, then 0 0 0 or Proteus	— 0 0	13	7	13	Improved after 7 days; then severe abdominal pain for 3 days (?perforation); intestinal hemorrhage twelfth and thirteenth days. Transfused 4 times	None	None?
M. E.	Stool	+×15; 0×5	+×1; 0×27	+	Stool culture positive 1 week after aureomycin begun; all others negative or overgrown by Proteus during therapy. Duodenal drainage, and stools 2 and 3 weeks after treatment ended were positive.				None	None
	Duodenum	—	+, 31	+						
	Stool	+	0	0	Bile cultures positive post-cholecystectomy until after second course was started. Stool cultures again positive after second course ended.				None	
	Bile	+×8	+, 1; then 0	0						
P. E.	Blood Urine Stool	0 0 +	0 0 0	0 0	2½	3	5	Diarrhea gradually stopped and improvement was then steady	None	Good
C. M.	Blood Urine Stool	0 + +	— — +	+, A +, A +, A	Operation before treatment started, bowel injected and distended. Bowel grossly normal at autopsy				None	Died
A. A.	Blood Urine	+ 0	+ —	+, A — Abscess +, A; Liver +, A	Slight improvement for 3 days, then chills, apathy and confusion returned. Hemoglobin dropped from 16 to 7 gm. Found dead in bed. Autopsy: ruptured aortic aneurysm (see "Diagnosis")				None	Died
F. S.	Blood	+×3	+×4; 0×5	—	Improved slightly for 3 days, mass got smaller and then was not felt; appetite improved and icterus cleared. Chills recurred; passed a bloody stool; hemoglobin dropped from 85 to 55% and patient died. No autopsy				None	Died

* + = positive, 0 = negative for causative organisms; A = autopsy; — = not done. The sensitivity of all strains isolated from the same patient before, during and after aureomycin were identical. Numbers after "+" or "0" in columns "During" and "After" = no. of days after treatment begun or ended, respectively.

† Relapse of fever during treatment suggested "drug fever"; test dose of 200 mg. after 10 days caused no fever or symptoms.

‡ Onset indeterminate; acutely ill at least two weeks prior to entry; aureomycin begun four days later.

from each of these sources. The patient's symptoms improved rapidly and he was afebrile at the end of the third day of treatment. It was felt at the time that improvement may have been due in some measure to the aureomycin therapy.

Patient J. H. (figure 2) was the infant sister of the first patient. She and other members of her family had been given typhoid vaccine by a local health officer while the first patient was still in the hospital. She became ill about three weeks after her brother had been admitted to the hospital and two days after the prophylactic typhoid vaccination. Interestingly enough, a

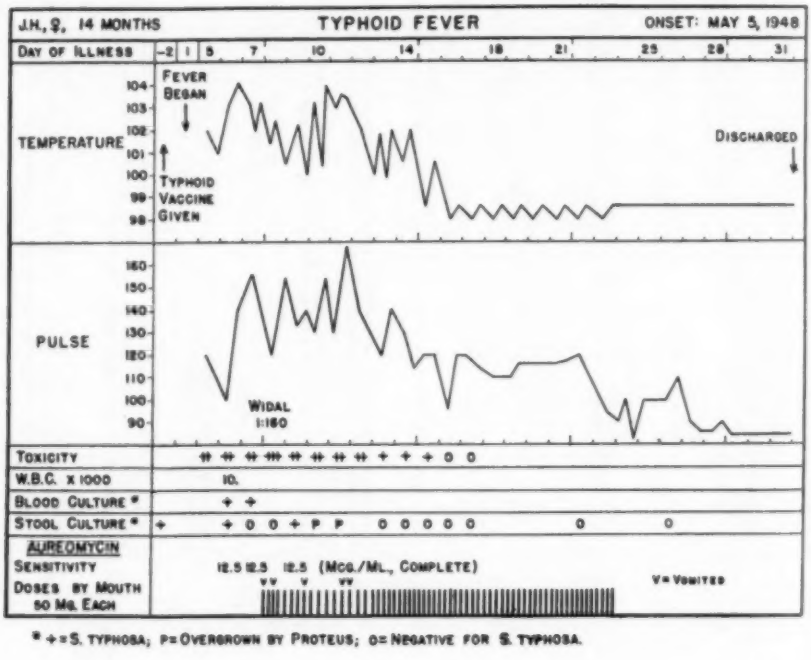


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FIG. 2.

culture of this patient's stool obtained by the health officer at the time of the vaccination was reported as positive for typhoid by the State bacteriological laboratory. Treatment was begun on the eighth day of illness, after positive cultures for typhoid bacillus had been obtained from both blood and stools in the hospital laboratory. No further blood cultures were obtained from this patient but of the numerous stools that were cultured during and after aureomycin therapy only the one obtained on the second day of treatment yielded typhoid bacilli; the others were either negative for typhoid organisms or were overgrown by proteus. The patient was not severely ill at any time, but definite improvement with a drop in temperature and pulse rate did not occur

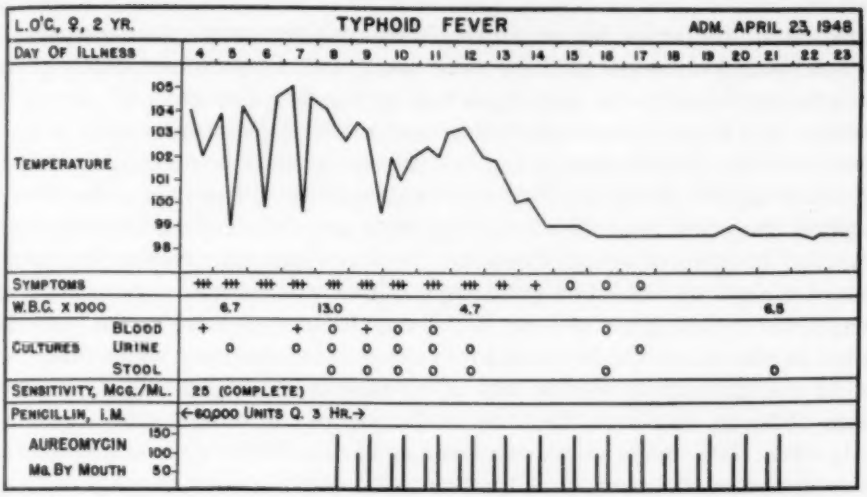
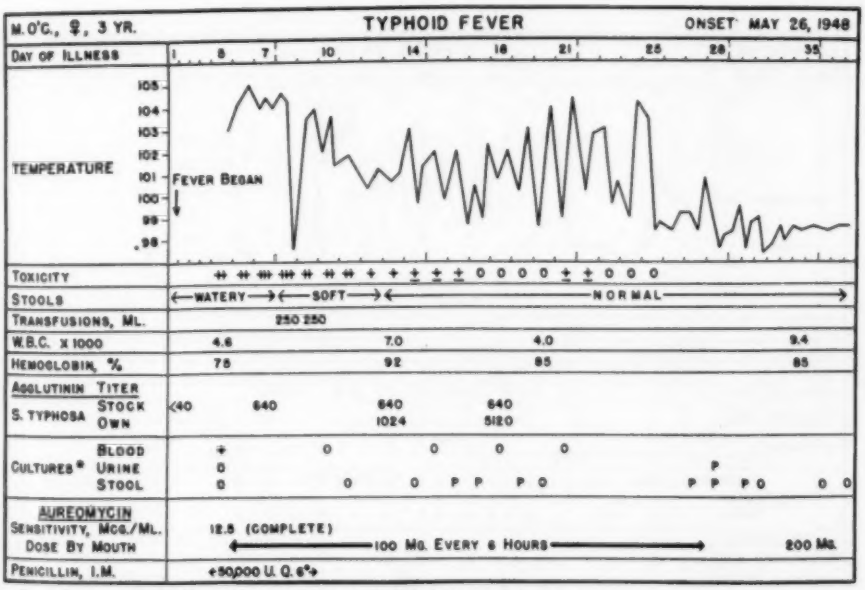


FIG. 3.



* +=S. TYPHOSA; P=OVERGROWN BY PROTEUS; O=NEGATIVE FOR S. TYPHOSA.

FIG. 4.

until after five full days of aureomycin therapy. It was felt that the aureomycin probably did not contribute much to the recovery in this case.

Patients L. O'C. (figure 3) and M. O'C. (figure 4) were members of the same family who were admitted to the hospital about a month apart. Blood cultures were positive before treatment in both of these patients and were all negative after treatment was begun except for one positive culture

obtained on the second day of treatment in L. O'C. All other cultures of blood, stool and urine before, during and after treatment were negative for typhoid bacilli but some of them were overgrown by proteus. Both of these patients continued to be acutely ill during the first five days of aureomycin therapy and then showed marked symptomatic improvement with a steady drop in fever. In the case of L. O'C. the temperature remained normal after the sixth day of therapy. Her sister's temperature, however, rose after the gradual drop and was then irregular until after the treatment was discontinued. In spite of fever, however, the latter patient remained essentially free of symptoms and had a good appetite and was therefore thought to have drug fever. A single oral dose of 200 mg. of aureomycin given a week later failed to reproduce the fever and its cause, therefore, remains in doubt.

It was difficult to ascribe any great benefit to aureomycin in these two cases although the favorable course during and after aureomycin, particularly in L. O'C. and the persistently negative cultures after the second day of treatment does not exclude the possibility that aureomycin was of benefit. It should also be noted that, except for the fever in M. O'C., all four of these patients were asymptomatic by the end of the second week of the disease.

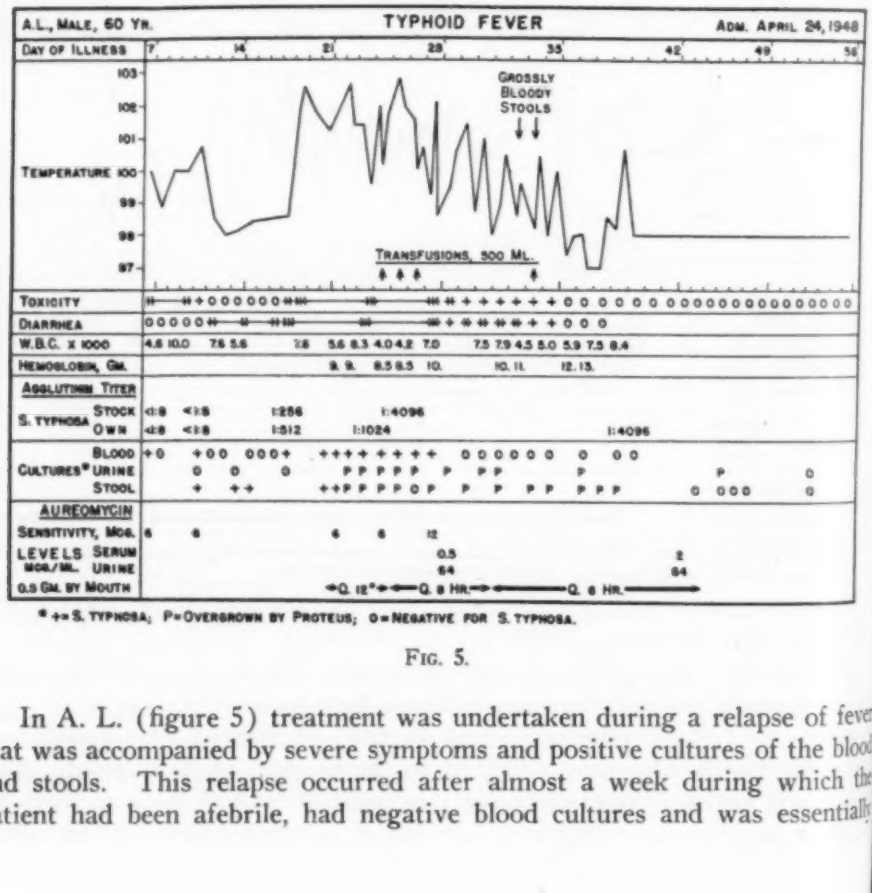


FIG. 5.

In A. L. (figure 5) treatment was undertaken during a relapse of fever that was accompanied by severe symptoms and positive cultures of the blood and stools. This relapse occurred after almost a week during which the patient had been afebrile, had negative blood cultures and was essentially

free of symptoms except for some diarrhea. The patient remained severely ill and continued to have positive blood cultures and severe diarrhea throughout the first week of aureomycin treatment. Thereafter he improved rapidly and blood cultures became and remained negative. During the period when his fever was declining the patient had severe abdominal pain and tenderness suggesting a perforation of the bowel but operation was withheld because of the marked improvement in the patient's general condition. He later passed some grossly bloody stools and was given transfusions. The aureomycin was continued throughout these episodes and improvement thereafter was steady. Stool cultures were positive before and on the first day after treatment was started but typhoid bacilli could not be identified in cultures of subsequent stool specimens, many of which, however, were markedly overgrown with proteus. Urine cultures in this patient were negative before treatment but the patient developed a lower urinary tract infection with *Proteus vulgaris* during a period when he was delirious and had an indwelling catheter. The bladder infection was mild, but persisted despite the aureomycin treatment until after the catheter was removed and other therapy was discontinued.*

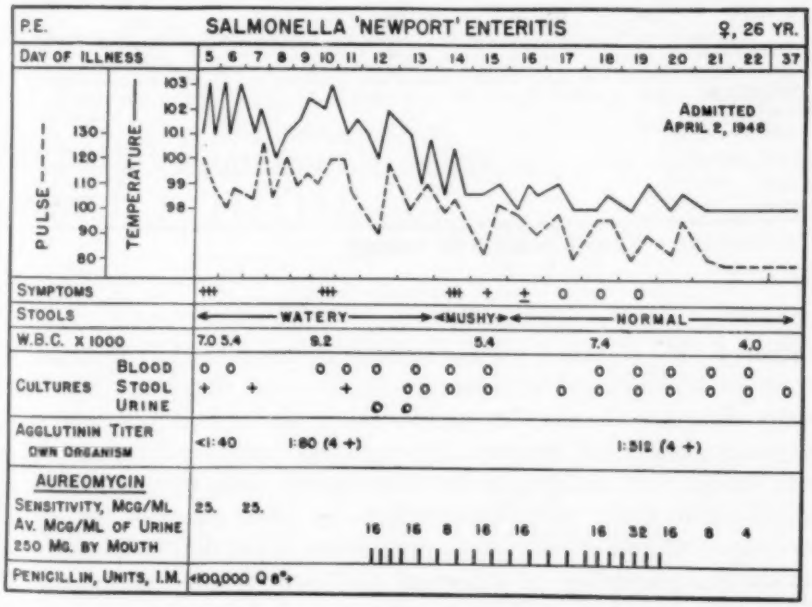


FIG. 6.

Salmonella Infections. Three patients were treated for severe salmonella infections. In P. E. (figure 6) aureomycin treatment was begun on the twelfth day of the disease when the patient was extremely ill with fever,

* *P. vulgaris* has proved most resistant to aureomycin in vitro and in vivo.[2, 4]

prostration and intense watery diarrhea and abdominal cramps. Blood cultures were all negative in this patient but cultures of three stools obtained before aureomycin treatment was begun were positive for *Salmonella newport*. The patient's temperature and pulse rate began to fall gradually and the abdominal cramps ceased soon after treatment was started. The stools became less frequent and less watery after the second day and were essentially normal two days later when the patient became and remained afebrile. All cultures of blood, stool and urine were negative for salmonella after treatment was started. Improvement in this patient coincided with the beginning of aureomycin treatment and may have been attributable to this therapy.

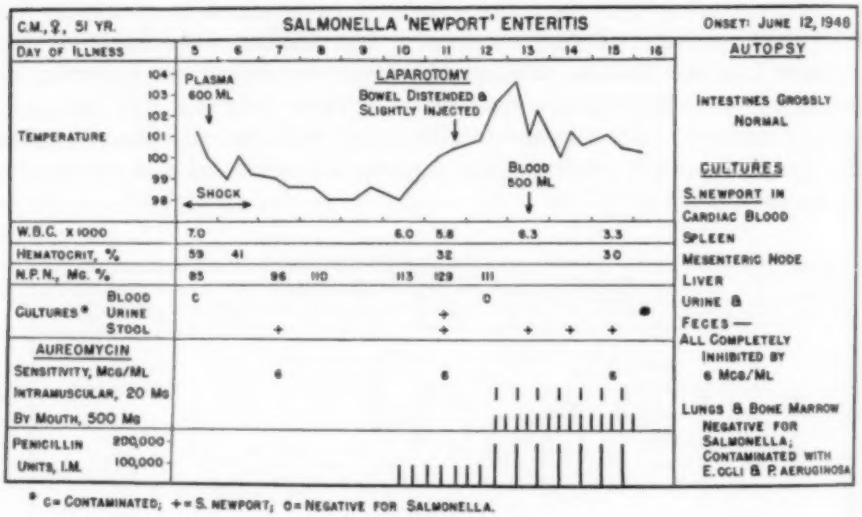


FIG. 7.

Patient C. M. (figure 7) was admitted on the fifth day of an extremely severe illness accompanied by constant vomiting and diarrhea. She had been markedly dehydrated and "in shock" with abdominal distention, rapid, thready pulse, low blood pressure, cyanosis and sweating for about 24 hours prior to entry. On arriving at the hospital the patient was treated symptomatically with fluids and plasma infusions. The cause of the symptoms was not apparent and in view of the persistence of the diarrhea, vomiting and distention the possibility of intestinal obstruction was considered. After much hesitation on the part of both internists and surgeons the patient had an exploratory laparotomy which showed no obstruction or other pathology that could account for the symptoms. Soon after the operation, however, cultures of one of the stools obtained earlier were reported as yielding a salmonella which was later identified as *Salmonella newport*. Additional cultures of blood, stools and urine were then taken and the patient was started on aureomycin by mouth and intramuscularly. The blood culture

was negative but the urine and stool cultures were positive for *Salmonella newport* and three additional stool cultures taken during the course of treatment were also positive for the same organism. Intramuscular penicillin was begun before the operation and was later continued because of signs that suggested the presence of congestion or infection in the lung. The patient failed to rally and died on the fourth day of aureomycin treatment.

At autopsy, there was moderate distention and some injection of the serosa and mucosa of the jejunum, the walls of which were soft and friable, but there were no hemorrhages. The rest of the bowel was grossly normal. Microscopic sections of various parts of the intestine all showed marked edema of all the layers with mild congestion of the vessels. There were also scattered foci of chronic inflammation in the submucosa of the ileum and colon. The mesenteric nodes showed some edema. There was vacuolization of all of the lining cells of the proximal tubules of the kidney which was interpreted as some kind of nephrosis. Autopsy cultures of blood, urine, feces and several organs yielded *Salmonella newport*.

Obviously, the aureomycin had no beneficial effect in this case, but the treatment may have been inadequate and was undertaken too late.

Patient A. A. (figure 8) was also acutely ill and in poor general condition on arrival at the hospital. The symptoms in this patient were referable to the mid-back and suggested a renal infection, but the urine was essentially normal and was negative on culture, and the blood nonprotein nitrogen was only slightly elevated. Blood cultures obtained before and during 11 days of oral and intramuscular therapy were all positive for *Salmonella suipestifer*. The patient had a steady drop in hemoglobin during this time but there was

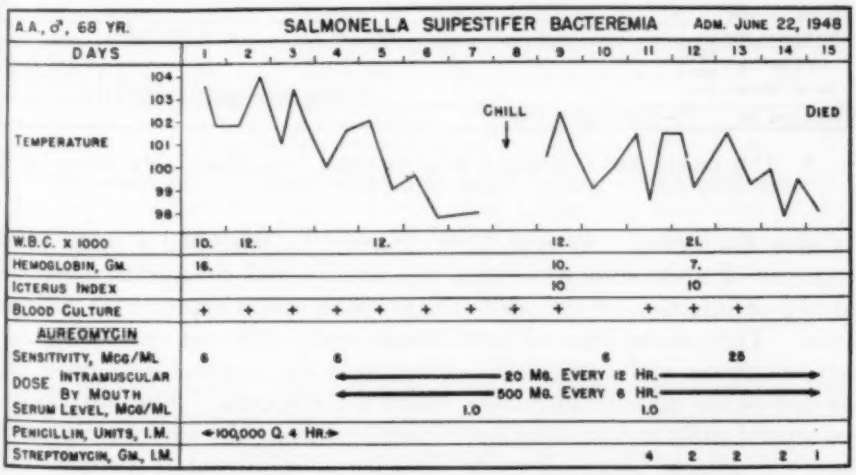


FIG. 8. This patient died of a ruptured aneurysm of the abdominal aorta. Autopsy also revealed bilateral psoas abscesses communicating with an intervertebral abscess in the lumbar spine. The cardiac blood, liver and pus from the abscesses all yielded positive cultures for *S. cholerae suis*. There was also a vegetation on one of the tricuspid valves, but a culture of this vegetation yielded no growth.

no evidence of bleeding from the bowel, and blood studies failed to reveal any evidence of intravascular hemolysis. Cultures of the stools failed to yield salmonella. The patient's general condition remained the same, but he died quite suddenly. Autopsy showed the death to be due to a ruptured aneurysm of the abdominal aorta with considerable extravasation into the retroperitoneal space. There were also large bilateral psoas abscesses communicating with an intervertebral abscess, the latter probably resulting from an osteomyelitis of the spine. *Salmonella cholerae suis* was obtained at autopsy from cultures of cardiac blood, pus from the abscesses, liver and other organs.

In this patient there was no evidence of any beneficial effect from the aureomycin on the local or systemic infection. Streptomycin was also given during the last four days without influencing the course of the infection.

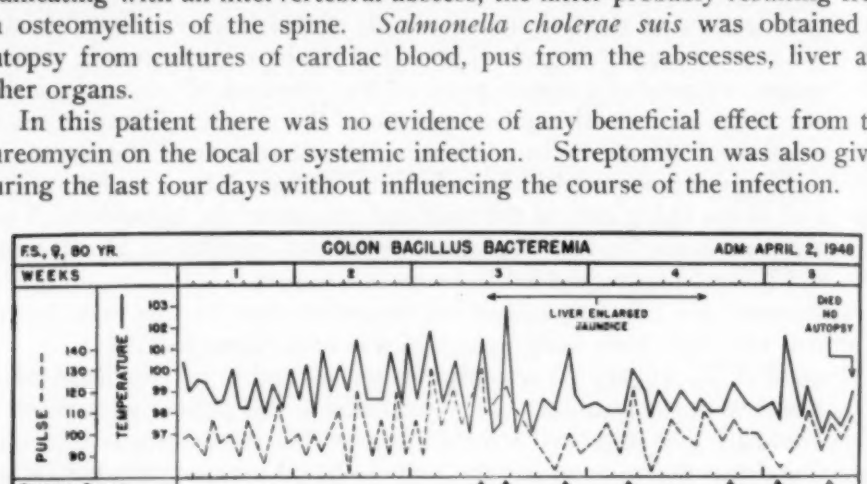


FIG. 9. This patient died following a large intestinal hemorrhage. The nature of the underlying disease and the source of the bacteremia were not determined.

Colon Bacillemia. Patient F. S. (figure 9), who had a colon bacillus bacteremia of undetermined origin, was acutely and chronically ill and had evidence of infection in the abdomen probably superimposed on malignant lesions. This patient showed some symptomatic improvement during aureomycin treatment with appreciable reduction in the size and tenderness of the liver and of the abdominal masses which were present. She did, however, have several chills and positive blood cultures during the aureomycin therapy. When the patient appeared to be sufficiently improved to permit further studies of the nature of the infection, she suddenly had a large intestinal hemorrhage and died. There was no autopsy so that the nature of the underlying disease was not determined. The temporary improvement in this pa-

tient may be attributable to the antibiotic, but the failure to sustain this effect was probably due to the presence of foci of suppuration that were unaffected.

Typhoid Carrier. Patient M. E. was a known carrier of typhoid bacilli for at least a year and was the probable source of an outbreak of typhoid fever in a nursing home which resulted in two deaths. At various intervals between August 1947 and April 16, 1948, 20 different stool specimens were cultured and 15 of them yielded typhoid bacilli. She was treated for 31 days with doses of 0.25 gm. of aureomycin by mouth every eight hours and stools were cultured daily during this period. Only one of them, obtained on the eighth day of therapy, was positive for typhoid bacilli; 22 were negative and seven were overgrown with proteus organisms so that typhoid bacilli, if present, could not have been detected. On the last day of treatment, duodenal drainage was carried out through a Levine tube and cultures of the drainage material yielded typhoid bacilli. In subsequent cultures of stools, typhoid bacilli were again obtained on June 1 and 8, two and four weeks respectively after the course of aureomycin treatment was ended. It was, therefore, evident that aureomycin alone had not accomplished the desired effect.

The patient had a cholecystectomy performed on July 19, and cultures of the contents of the gall-bladder and of the common duct bile obtained at the operation were both positive for typhoid bacilli. Biliary drainage was then carried out through a T tube and daily cultures of the biliary drainage fluid continued to be positive. On July 26, the patient was again started on aureomycin by mouth; 1 gram was given every six hours for four doses and then 0.5 gram every six hours until August 4. Cultures of bile were positive before the first dose and again on July 27 but they were negative on July 28 and thereafter. Stool cultures failed to yield typhoid bacilli during the second course of aureomycin, but many of them were overgrown by proteus. The stools again became positive one week after the aureomycin was stopped.

Tests made with bile obtained from this patient on many occasions before and during the aureomycin treatment indicated that the bile itself did not inactivate aureomycin when added to a solution of the antibiotic in vitro. It was not possible, however, at any time during the treatment to demonstrate aureomycin activity in bile obtained from the T tube even when care was taken to test for this activity promptly after the bile was obtained.

Toxicity

Except for possible drug fever in L. O'C., there was no evidence of any toxic effects attributable to aureomycin in any of these cases. Patients J. H. and M. O'C. vomited some of the early doses, but they had been vomiting more or less constantly before the treatment was started. It is of interest that the diarrhea that was present in some of these patients improved while they were taking aureomycin. In other groups of cases, the occurrence of large bulky stools was almost the only untoward effect from oral aureomycin.[1, 4] There

was no evidence of any toxic effects on the blood, kidney or liver in any of these patients and no rashes were observed.

Discussion

The present cases indicate quite clearly the need for caution in interpreting the results of the use of any new therapeutic agent in many infectious diseases. The results of therapy in two of the patients with typhoid fever, R. H. and L. O'C., and in one of those with salmonella infection, P. E., could be considered as indicating definite beneficial effect from aureomycin. These patients began to improve within a day of two of the time when the antibiotic was begun, and all of their cultures were negative for the causative organisms after treatment was started, except for one positive blood culture obtained after 18 hours in patient L. O'C. The course of events in two of the other typhoid patients, J. H. and M. O'C., likewise could be interpreted as showing some favorable effect in that improvement, both clinical and bacteriological, began after treatment was started and was progressive, though slow, thereafter. The persistent fever in the case of M. O'C. was not accompanied by any relapse of symptoms. Even in the case of patient A. L. who was so severely ill and continued to have positive blood cultures throughout the first week of treatment, it was felt that the aureomycin may have had some favorable effect in limiting the severity of the illness and may possibly have averted what was expected to be a fatal outcome.

The failures to influence the clinical course or the bacteriological findings of the salmonella enteritis in patient C. M. may, of course, have been due to the fact that treatment with aureomycin was undertaken when the disease was far advanced and the patient already had renal failure with nitrogen retention, possibly resulting from the dehydration and shock. In the case of A. A., on the other hand, while the death was not directly attributable to the infection, the failure to control the latter was associated with the presence of large foci of suppuration that were not detected before death. The same was probably true in the case of the colon bacillus bacteremia, although absolute proof for this is lacking. The failure to eliminate the carrier state in M. E. before the cholecystectomy was performed may also have been due to the inability of aureomycin to influence the focus in the gall-bladder. Furthermore, it was not possible later to detect aureomycin activity in the bile of this patient while she was receiving fairly large doses of the antibiotic by mouth. The failure in this case may be attributable to persistence of infection in the liver and bile ducts and the failure of the antibiotic to clear these foci of the organisms.

It can only be concluded that the effects of aureomycin in the present group of cases leave much to be desired. The possibility cannot be excluded that the use of larger oral doses, or parenteral therapy in proper doses may have a better effect in such cases.

The recent preliminary report of favorable effects from chloromycetin on typhoid fever,[11] when carefully scrutinized, also does not give unequivocal evidence of benefits ascribable to that antibiotic. The types of cases, severity and other details are not given in this preliminary report. These details and the results in additional cases, particularly severe and late cases, are awaited before final judgment of the effects of this agent can be made.

Summary and Conclusions

The relevant features in five cases of typhoid fever, three of severe salmonella infections, a case of colon bacillus bacteremia and a typhoid carrier that were treated with a new antibiotic, aureomycin, have been presented. The clinical and bacteriologic findings in some of these cases suggested that the aureomycin had some beneficial effects, but the results, in general, were not striking. Concealed foci of suppuration may have been responsible for some of the failures.

Addendum. Two additional cases of typhoid fever treated since this paper was submitted are worth mentioning:

M. F., a white woman 39 years old, was started on aureomycin therapy on the ninth day of illness. She was acutely ill and disoriented, with fever ranging between 103 and 105°, nausea, vomiting, diarrhea, repeated showers of rose spots and an enlarged liver. She had received 5 gm. of sulfathalidine every four hours and a million units of penicillin every three hours for seven days but her clinical condition failed to improve on this regime, and on the night of the eighth day, she suffered a massive intestinal hemorrhage. Other chemotherapeutic agents were then discontinued and aureomycin was given in doses of 1 gm. orally every four hours. After four days, the dose was gradually reduced to 2 gm. daily and she received a total of 90 gm. in 25 days. The patient improved promptly after the aureomycin was started. The temperature fell to normal by lysis during the course of one week; no further rose spots appeared; the diarrhea abated; no further intestinal hemorrhage occurred, and the stools became normal in the space of a few days. Repeated blood, urine and stool cultures were negative for typhoid bacilli during the aureomycin treatment and for three weeks thereafter with the exception of a single positive stool reported on the twenty-third day of treatment; on the same day, however, bile obtained by duodenal drainage was negative for typhoid bacilli.

H. W. K., a white male of 29, was started on treatment with aureomycin on the seventh day of a severe relapse of typhoid during which he was having repeated chills, fever sustained at 105 to 106° F., delirium, rose spots, nausea, intense diarrhea, jaundice and positive blood and stool cultures in spite of treatment with 6 gm. of sulfadiazine and 8,000,000 units of penicillin daily. This therapy was then discontinued and 0.5 gm. of aureomycin was given every four hours. Within 12 hours the temperature dropped to 101° F., and then gradually to normal over the following week; the patient's sensorium cleared; no further rose spots appeared; stools became less frequent and semi-formed and then formed; jaundice cleared; and all cultures of blood, urine and stools were negative after the treatment with aureomycin was started.

In M. F., aureomycin seemed to have a definite beneficial effect, although the significance of the single positive stool culture during treatment is not clear. In H. W. K. it was felt that the clinical and bacteriological improvement was definitely related to the aureomycin therapy. The findings in the latter case are in sharp contrast to those in patient A. L. (figure 5) in whom the course prior to aureomycin was very similar, but smaller doses of aureomycin were used and the bacteriological and clinical recovery were considerably more delayed. These two cases, however, serve only to reëmphasize the difficulty in evaluating the efficacy of this agent even when relatively large doses are used by mouth.

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INFECTIOUS ARTERITIS *

By WILLIAM S. MIDDLETON, F.A.C.P., *Madison, Wisconsin*

THE anatomico-physiological relationships of arteries presuppose not only their normal nutrient responsibility but also repeated exposures to adverse influences, such as physical, chemical, toxic, and infectious, that affect tissues and organs generally. The degenerative conditions of the arteries have received increasing attention in the laboratory and the clinic in recent years. The inflammatory states of these vessels have not been accorded proportional attention. In fact the clinical appreciation of infectious arteritis has lagged far behind the advances in the knowledge of the pathogenesis and pathology of this significant group of vascular injuries.

The arterial walls may be the seat of degenerative changes in the course of a number of infectious diseases. Fatty degeneration in the intima and media may occur in typhoid fever, brucellosis, scarlet fever, pneumonia, and diphtheria. These degenerative changes may be attended by a subintimal proliferation. Although this reaction is non-specific, the vascular injury may lead to rupture and severe hemorrhage. Rarely does arterial thrombosis attend this lesion. The histologic common denominator of a fibrinoid degeneration of collagen has led to an interesting grouping of lupus erythematosus disseminatus, dermatomyositis, scleroderma, and Libman-Sacks' syndrome.[1] Baehr and Pollock [2] stress the fallacy of too close analogies on this ground and on the basis of clinical dissimilarity separate rheumatic fever, rheumatoid arthritis, serum sickness, periarteritis nodosa and thromboangiitis obliterans from disseminated lupus erythematosus and scleroderma. Certain fine points of microscopic differentiation, as the "wire loop" lesion in the glomeruli in lupus erythematosus disseminatus, might be invoked [3]; but for present purposes Klemperer's position [4] of the non-specificity of diffuse collagen diseases with an incidental vascular involvement excludes their consideration in this relation.

Inflammation of the arteries may occur by continuity. Yet the arterial wall must have a high degree of tissue resistance, since in many instances arteries traverse zones of virulent infection and active inflammation without intrinsic involvement. However, the arteries may be attacked by infections from within or from without. By the former route a septicemia is usually responsible. In plague, for example, the blood stream may be heavily seeded with *Pasteurella pestis* and the vascular injury be widespread. In pyogenic infections a septic embolus is the source of a local vegetative endarteritis, which may lead to a mycotic aneurysm or to rupture with more or less serious results. If the invasion be from without, a periarteritis with in-

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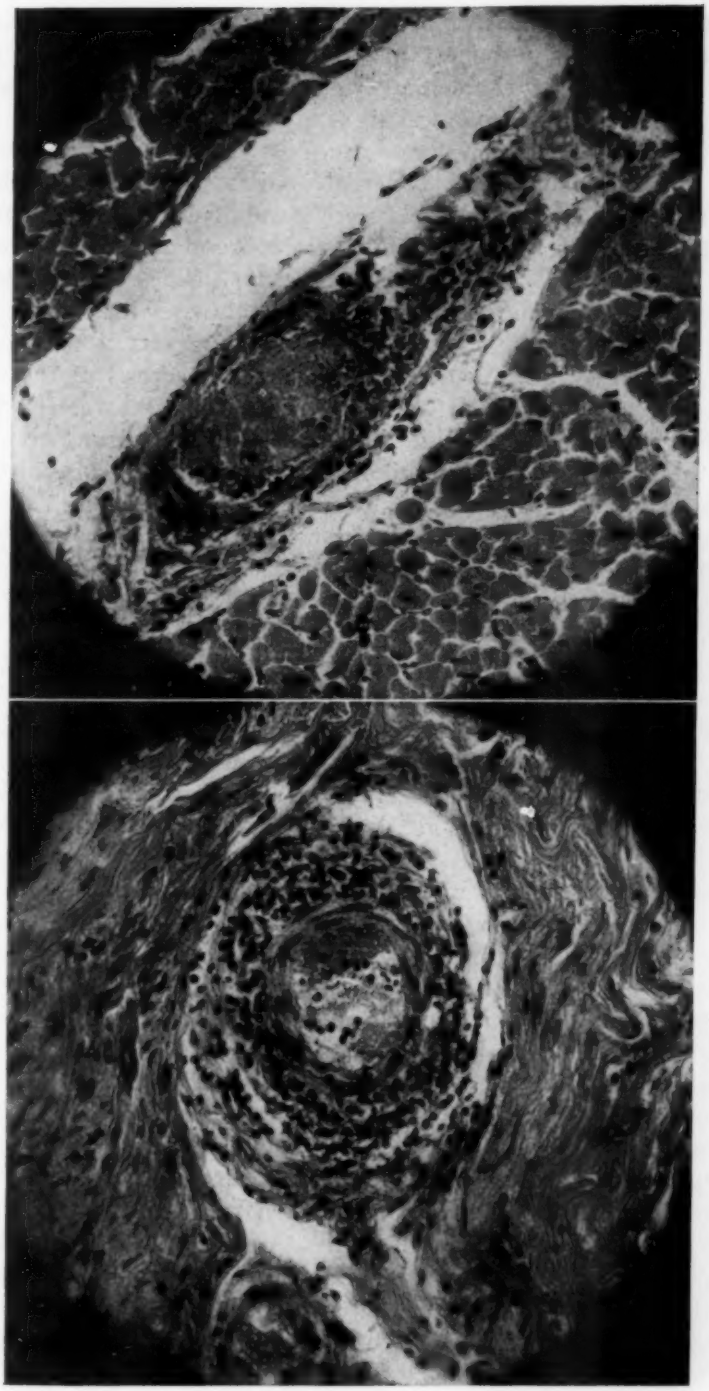
volvement of the adventitia, media, and intima in sequence may be anticipated. The perivascular lymphatics may bear the infective organisms to the arteries. The cellular infiltration may similarly weaken the wall with disastrous effects. Whether perivascular or endovascular, lesser degrees of reaction may lead to thrombosis. To project the functional consequences of such lesions, the nutritional changes incident to such encroachments upon vascular channels may well persist after the clinical subsidence of the pathologic process.

In general the pathogenesis of infectious arteritis depends upon the direct invasion of the vessel by the etiologic agent. A further important mechanism, hyperergy to streptococci, was suggested by Swift, Derick, and Hitchcock [5] in explanation of the rheumatic lesions. Gruber [6] had earlier advanced the same thesis for the pathogenesis of periarteritis nodosa. Rössle [7] broadened this concept by indicating the non-specificity of the etiology for periarteritic reactions. Clark and Kaplan [8] observed analogous changes in mesenchymal tissues with periarteritis and necrotizing arteritis after large doses of antipneumococcus serum. More recently Rich [9, 10] and his associate Gregory have demonstrated beyond peradventure the dependence of periarteritis nodosa upon sensitivity. Interesting has been the incrimination of sulfonamides in this relation.

The rickettsial diseases afford the best examples of widespread vascular injury in the course of acute infections. The primary reaction to the *Dermacentroxenus rickettsi* of Rocky Mountain spotted fever is a swelling and proliferation of the endothelium of the capillaries, arterioles, and veins. Perivascular infiltration with monocytes, lymphocytes, and plasma cells occurs. The rickettsiae are abundant in the endothelium and the muscularis media of the affected vessels. Thrombosis is common and may lead to gangrene of the soft palate, ears, nose, fingers, toes, buttocks, prepuce, scrotum, and vulva. In a word the basic lesion of Rocky Mountain spotted fever is an infectious endangiitis (figures 1a and b). The skin and the central nervous system are predominantly involved, but the vessels of the thyroid gland, gastrointestinal tract, myocardium and skeletal muscles are occasionally affected. Hemorrhages into the skin, subcutaneous tissue and testis, with the described gangrene, constitute the sole gross lesions.

The cutaneous manifestations of Rocky Mountain spotted fever strongly suggest their vascular background. The early macular eruption over the wrists, ankles, and back becomes generalized. Subcuticular blotching depends upon an interference with the circulation in the deeper layers of the skin. Extravasation of blood into the eruption puts an end to blanching on pressure. Duskiness of the dependent legs and edema of the hands and feet reflect venous impairment or deep thrombosis. Gangrene is a frequent sign of more serious arterial involvement. The eruption, upon fading, may leave a residual pigmentation which lights up on vascular dilatation or pales upon vasoconstriction long after convalescence. Desquamation is not an infrequent sequel to the eruptive phase. Reflecting the predilection for the central



(a) Skin (b) Myocardium

FIG. 1. Histologic lesions of Rocky Mountain spotted fever.

nervous system, restlessness and insomnia may obtain. Delirium may give way to coma. Photophobia, stiff neck, muscle resistance, positive Kernig sign, and convulsions may suggest meningeal involvement. Cloni, paradoxical reflexes, deafness, and speech involvement may imply focalization, but with few exceptions these neurological signs are transitory.

Periarteritis nodosa has been one of the most elusive of the diseases attended by serious vascular injury. Recent studies [7, 8, 9, 10] have elucidated certain aspects of its pathogenesis. Hyperergy undoubtedly plays a major rôle in its initiation. Infection, rheumatic, streptococcal and pneumococcal,[6, 7, 11] has been incriminated in this relation. Serum sickness [8, 10] and hypersensitivity reactions to chemicals [9, 10] are other cogent bases for this astounding pathologic picture. The histologic sequence suggests a perivascular lymphatic portal. The fundamental changes include necrosis of the media and fibrino-cellular infiltration of all coats of the involved vessel. Lymphocytes, plasma cells, and eosinophiles dominate the cellular exudate. Proliferation of the lining endothelium follows. This intimitis leads to thrombosis in many instances. With organization these thrombi become canalized. With disintegration of the muscularis and the elastic lamina tiny aneurysmal protrusions may ensue. Fibroblasts are replaced by fibrous tissue as repair advances. The encroachment upon the local nutrition may induce atrophy, degeneration, infarction, gangrene, and scarring (figure 2).

The distribution of periarteritic lesions is singularly bizarre and irregular. An isolated vessel may be involved; but contrary to the earlier opinions temporal arteritis may at times be a superficial manifestation of a widespread involvement.[12] These circumstances, together with the several stages of the pathologic process in the same subject, presage an inconstant clinical picture. However, all symptoms and signs are directly traceable to the inflammation, disintegration, and repair of the arterial tree. Indeed, the impairment of nutrition may be much greater in the stage of repair than in the active inflammation. The diagnostic tetrad of Meyer [13] and Brinkmann,[14] chlorotic marasmus, polyneuritis and polymyositis, vague gastrointestinal disturbances and nephritis, affords an excellent spring-board for the clinical diagnosis. The muscular and neural manifestations are directly attributable to the periarteritic lesions. Invasions of the coronary bed may lead to thrombosis. Bronchial asthma may occur in a causal or incidental relationship. A variety of symptoms and signs attends the involvement of the abdominal arteries. Among these the predilection for the vessels of the gall-bladder may bring the strong suspicion of acute cholecystitis in its train. Duodenal ulceration with all of its clinical picture may arise from periarteritis nodosa. Diabetes mellitus may reflect pancreatic involvement. A rising blood pressure with the evidences of renal insufficiency bespeaks an extensive invasion of the arteries of the kidney. Nor would a recital of the central nervous and cutaneous manifestations exhaust the clinical potentialities of this condition. Most important in the recognition of periarteritis nodosa is a diagnostic awareness. A wide dispersion of vague symptoms and signs in a septic

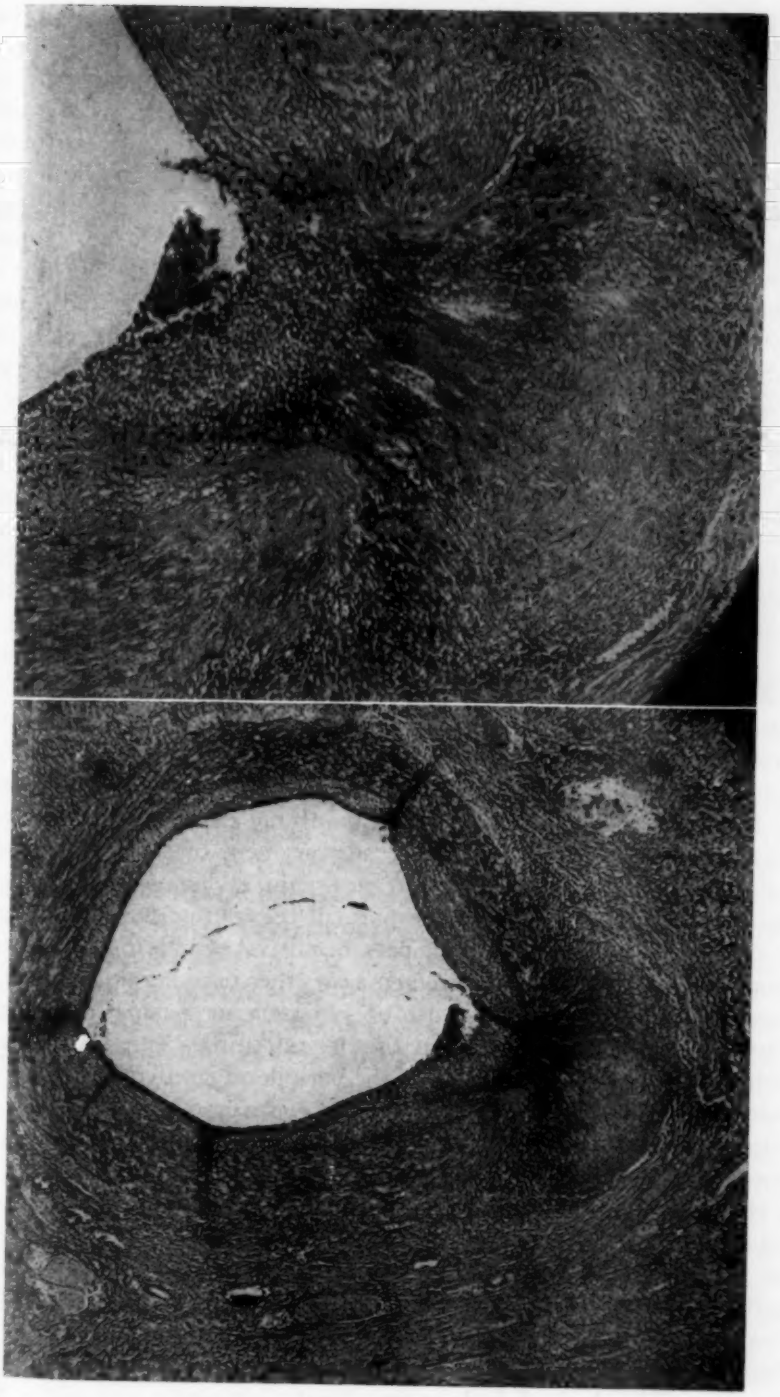


FIG. 2. Histologic lesion of periarteritis in the liver. Left × 15; right × 40. (Courtesy of Dr. Norman J. Sweet, San Francisco)

patient should suggest the diagnosis, since only by a diffuse vascular process could such a clinical picture develop. Eosinophilia, among other laboratory findings, is a further signpost to its consideration.

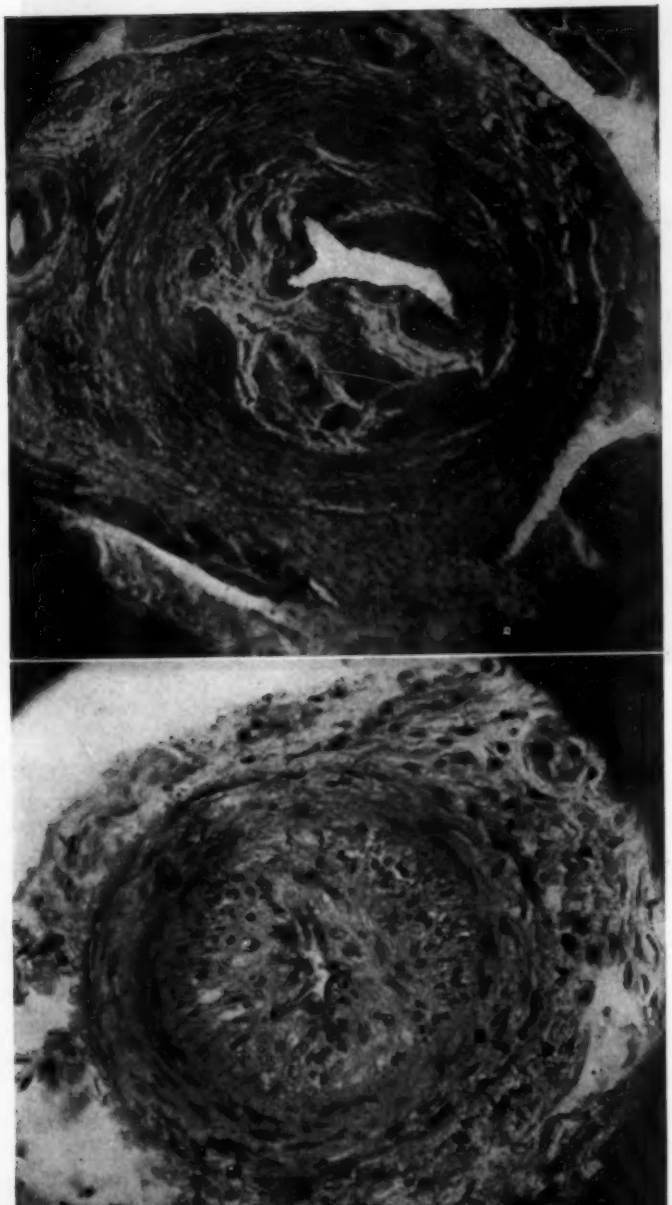
Although other etiologic factors have been invoked, thromboangiitis obliterans would seem to be infectious or allergic in origin. Essentially a disease of the extremities, it is also encountered in the cerebral, coronary, mesenteric, and renal arteries. The moderate sized arteries of the leg are more commonly involved than those of the thigh. A minority of sufferers from this disease undergo invasion of the arteries of the arm. Intimal proliferation usually initiates the pathologic process. Occasionally the adventitial infiltration is primary. In the acute phase lymphocytic and neutrophilic invasion of all coats of the artery may be observed. Giant cells may appear. Significantly the arterial changes are segmental and considerable spans of an affected vessel may escape. Thrombosis occurs at the site of vascular inflammation. These thrombi contain inflammatory cells but tend to undergo organization after fibroblastic infiltration. Canalization of the thrombus follows and mere slits of tiny communicating lacunae promise a meagre approximation to the pre-inflammatory nutrition for the involved part. The veins of the leg become similarly involved. Migratory phlebitis is the rule. In spite of the segmental involvement recurrences of inflammation insure progressive circulatory incompetence in the part in most instances. Eventually the involved artery, vein and nerve become incorporated in a single inseparable cord (figure 3).

Thromboangiitis obliterans first reflects itself clinically in unusual coldness, paresthesias, pallor and cyanosis upon exposure to cold. This circumstance may mean unusual vasospasm to ordinary stimuli in susceptible vessels. Muscular weakness and aching pains on effort may early result from vascular encroachment. With the advancement of this process intermittent claudication may give place to rest pain. Changes in the color, temperature, texture and pulses of the part all reflect the degree of arterial injury. Anginal episodes may anticipate occlusive symptoms in coronary involvement. Quantitative measurements of the peripheral vascular integrity are now available. By release of sympathetic spasm the degree of actual organic change in the arteries of the extremities can be estimated. Such studies will disclose impairment of the peripheral circulation long before trophic ulceration and gangrene mark the final, irreversible stages of the disease. Furthermore, the intrinsic control of the arterial tone may persist or be resumed after radical sympathectomy.

The rheumatic state is still incompletely understood. Several material gaps in the complete picture remain unfilled. The streptococcus is presumed to be the etiologic agent and a bacterial hypersensitivity has been invoked in its pathogenesis. Certainly from a clinical standpoint this thesis finds substantial support. Furthermore on this basis its common chronicity and its far flung pathologic expressions find much readier explanation than in the older theories. The Aschoff body is the specific histologic unit of the rheu-

FIG. 3. Histologic changes of thromboangiitis obliterans in vessels of leg.

matic state. Always this characteristic agglomeration is closely associated with arterioles. The fibrinoid swelling of the ground substance anticipates the cellular reaction, but it is not specific to the disease. In the vascular injury of the rheumatic state the lesions are widely scattered and variant in intensity. The arteries may be involved in many organs and tissues. Again only isolated branches within a given organ are affected. Endothelial swelling with exfoliation suggests luminal invasion. Thrombosis is rare in rheumatic arteritis. A fibrinous exudate may infiltrate the arterial wall and invade the supporting tissues with a loss in the continuity of the elastica. Thereupon necrosis of the wall with extravasation of blood may ensue. The cellular reaction is neutrophilic and macrophagic. Lymphocytes, plasma cells, occasional eosinophiles and young fibroblasts complete the zone of cellular reaction. Whereupon there occurs an astounding revascularization. New vascular channels appear in the described fibrinous exudate in the walls of the affected artery. As this exudate disappears the muscularis is lost and the elastic laminae are approximated (figure 4a and b). Rheumatic aortitis arises through involvement of the vasa vasorum. Lymphocyte and plasma cell infiltration of the adventitia leads to medial ischemia. Linear fibrosis may impair the elastic and muscular coats but rarely is there serious injury comparable to syphilis.



(b) Coronary

(a) Pulmonary

FIG. 4. Histologic changes of rheumatic arteritis.

Rheumatic fever has lost its old connotation of a disease limited to the synovial and serous membranes and the heart. Few tissues escape its wide attack. Singularly by the terms of its hyperergic pathogenesis, such sensitized subjects are doomed to recurrent, if not continued, onslaughts of the disease. Not only is its victim crippled in the extent of its initial involvement, but there is also the threat of an extending handicap from the vascular encroachment of healing. The initial verrucose vegetations of rheumatic valvulitis eventually undergo cicatricial contraction with resultant insufficiency and stenosis. Contributory to the permanent changes in the valves are the nutritional disturbances of arterial injury—and the coronary arteries, probably, never escape rheumatic involvement. Furthermore, by the same token, the myocardium feels the weight of rheumatic infection and progressive or deferred myocardial fibrosis may be predicted. In general clinicians have a sound viewpoint relative to the gravity of the ultimate prognosis of rheumatic heart disease. Its explanation resides in the insidious order of the rheumatic invasion and repair. Acute and recurring episodes leave residua that pyramid the functional handicap of the original attack.

Syphilis is admittedly a vascular disease. The spirochetes enter the vessel by way of the vasa vasorum or the perivascular lymphatics and the lesion in the smaller arteries is primarily periarteritic. A collar of lymphocytes and plasma cells encircles the involved vessels. Occasionally a distinct gumma is discerned. Medial involvement induces atrophy of the muscularis. Endothelial swelling with proliferation appreciably reduces the lumina of the small arteries (figure 5). Aneurysmal dilatation on a syphilitic background is unusual in the muscular arteries in contrast to its high incidence in syphilis of the aorta, where the disintegration of the preponderant elastica establishes the susceptibility to dilatation. Thrombosis may attend the intimal injury.

During the period of clinical latency some inflammatory changes persist in the vascular system. Lymphocytes and plasma cells resist the encroachment of the spirochetes from the perivascular lymphatics. The endarteritic process advances inexorably and the illusion of arrest may be shattered by delayed evidences of nutritional disturbance and degeneration in the parts supplied. While any viscus may be involved, the leptomeninges and aorta afford the most classical examples of late syphilitic involvement. Significantly the delay in clinical manifestations resultant upon such invasion can more properly be attributed to local tissue resistance than to deferred pathologic reaction.

"Their slow combined inflammatory degeneration *ages the patient* by inducing a premature fibrosis, and it threatens physical integrity and impairs the functional capacity of his vital structures by destroying their vital substances and replacing it with connective tissue." [15] Precocious cerebral accidents suggest a syphilitic etiology. In cerebral vascular involvement alterations in the habit of thinking, irritability, psychic changes and obscure head-

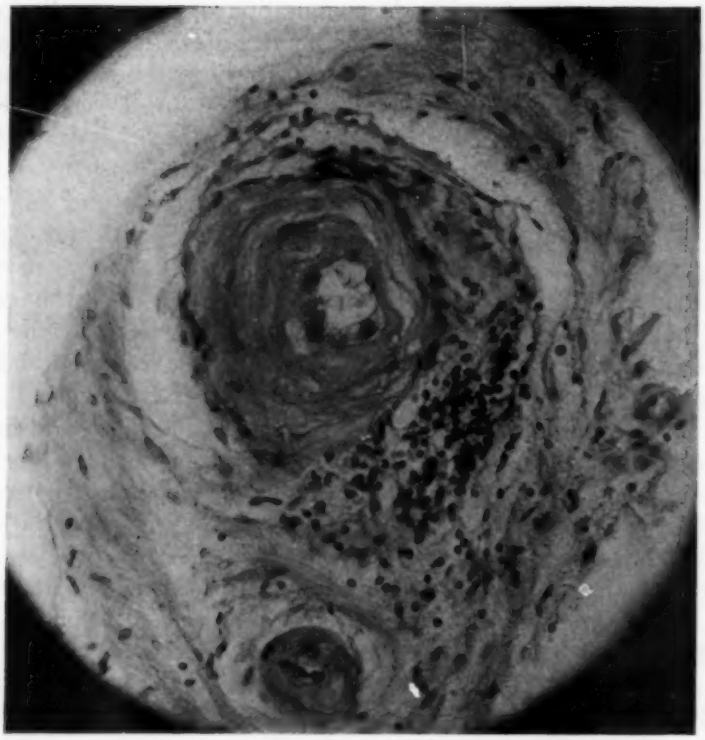


FIG. 5. Histologic lesion of syphilitic arteritis (leptomeninges).

aches or vertigo may anticipate the vascular accident. Visceral involvement elsewhere may encompass the whole gamut of symptomatology.

In summary, the problem of infectious arteritis may be assessed as involved and neglected in the main.[16] The order of histologic changes of the arterial tree gives the clue to the route of invasion. The clinical course of certain diseases depends predominantly upon the specific inflammatory arteritis. In others its place is subsidiary. The reparative stage of certain forms of infectious arteritis may be more significant than the active inflammation. Infectious arteritis forms the dominant feature of the rickettsial diseases, periarteritis nodosa, and thromboangiitis obliterans. In all of these diseases the entire picture may be interpreted in terms of the extent and the degree of the vascular injury. The acute inflammatory phase of the infectious arteritis determines the clinical expression of the rickettsial diseases and its subsidence marks the period of recovery in their course. Undoubtedly permanent changes in the smaller arteries remain as relics of their earlier inflammation, but in the main they are unimportant. Periarteritis nodosa and thromboangiitis obliterans are characterized by just as specific vascular changes, but importantly in these diseases the processes of repair determine even more serious nutritional changes in the involved part than

does the acute infectious phase. Rheumatic fever and syphilis represent a somewhat different situation. The inflammatory stage of the infection is not frequently an independent dominant feature of rheumatic origin; nor is the vascular injury prone to induce aneurysmal dilatation in the small vessels. The effects of rheumatic and syphilitic arteritis are dependent upon long continued subnutrition with degeneration and fibrosis rather than the pathological changes of the acute vascular damage.

Note: Grateful acknowledgment for the preparation of the photomicrographs is made to Drs. J. C. McCarter and J. J. Lalich.

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CORAMINE (NIKETHAMIDE) IN BARBITURATE POISONING: COMPARISON WITH PICROTOXIN; PRELIMINARY REPORT *

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Recently a marked increase in the number of cases of poisoning due to barbituric acid derivatives has made an effective antidote or analeptic a matter of paramount importance. The drugs of the barbiturate group have been readily available to the laity, and newspaper publicity, instead of helping the situation, appears actually to have increased the number of cases of attempted suicide from these drugs.

Various antidotes for human barbiturate poisoning have been in use for years. Picrotoxin and coramine (as coriamyrtin) were used as early as 1891–1892.[1] Arnett [2] administered picrotoxin in 1933 after Maloney, Fitch and Tatum [3] had demonstrated its effectiveness in animal experiments. Koppanyi [4] used it extensively in 1936. Burdick and Rovenstine [5] in 1945 claimed picrotoxin to be the drug of choice in barbiturate poisoning. Unfortunately this has tended to result in the neglect of other drugs, one of which, coramine, we believe to be equal to, if not superior to picrotoxin.

In order to demonstrate the practical use of coramine in those barbiturate intoxication patients having a degree of narcosis approaching lethal levels, to establish the proper dosage, to determine the margin of safety, and to establish important prognostic criteria in these poisoned patients, the study of this analeptic drug was undertaken. Throughout the study, coramine was compared with picrotoxin. No attempts were made to use metrazol, amphetamine sulfate, strychnine or any combination of these in this series. The cases were graded as to the depth of narcosis, since too many reports make no effort properly to evaluate this factor.

The cases were divided into two groups: those patients admitted to the hospital on even numbered days were treated with coramine, and those admitted on odd numbered days were treated with picrotoxin. A few cases received both coramine and picrotoxin, when heroic measures were thought necessary. In 1945 and 1946, a total of 58 cases were treated, with five deaths. From 1941 to 1945, there were 41 cases with three deaths, a total of 99 cases with eight deaths in five years.

Coramine (also known by the official non-proprietary name of Nikethamide) is pyridine betacarboxylic acid diethylamide, a yellowish liquid, freely soluble in water. The ordinary ampule is 1.5 c.c. of 25 per cent solution. In 1892 Koppen [1] reported its use in the counteraction of narcosis under the name of coriamyrtin. Coriamyrtin occurs in several species of the plant

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Coriaria, of which the best known is *Coriaria myrtifolia* or currier's sumach. (Coramine as used today is a synthetic compound, not the extract of Coriaria as originally used.) Further investigations in European countries were reported by Uhlman,[6] Guth,[7] Schubel and Gehlen.[8] Kennedy [9] in 1932 reported in the English literature on the use of coramine in avertin narcosis. Wood [10] in 1933 and Levi and Krinsky [11] in 1936 further emphasized its value. The latter authors found, in studying the effect of coramine on postpartum patients under the influence of barbituric acid drugs, that it greatly shortened the postpartum narcosis period and that patients in extremis after administration of nembutal and paraldehyde recovered after treatment with coramine. Schube,[12] studying the effects of coramine on patients in a mental institution who had received over-doses of phenobarbital, found it effective as a life saving analeptic (1936). P. G. Fratten [13] noted in 1940 that coramine appeared to be the best drug in the prevention and therapy of complications of intravenous barbiturate narcosis. Harris et al.,[14] reporting recently, used coramine in a case in which a young woman had taken 125 grains (8.1 gm.) of phenobarbital resulting in four days of coma. Picrotoxin seemed ineffective and "coramine was then administered intravenously when a fatal termination seemed inevitable." Improvement was steady and the patient recovered.

Coramine (Nikethamide) is a quick acting analeptic, vasopressor and respiratory stimulant. Its action is primarily on the higher brain centers although all portions of the cerebrospinal axis, respiratory, vasomotor and vagal centers of the medulla, and the cerebral cortex are affected. It thus helps to restore normal vascular tone, increase cardiac efficiency, deepen respiration and combat anoxemia. Frequently repeated doses of coramine as used, are not cumulative in producing convulsions; on the other hand picrotoxin, repeatedly administered, tends to cause convulsions which can be combated only by further administration of barbiturates. Androp [15] feels that picrotoxin is contraindicated where large doses are needed for therapy because of the danger of convulsions. Freireich and Landsberg [16] have described unsatisfactory experiences with picrotoxin in the treatment of acute barbiturate poisoning, mainly because of the production of convulsions.

Method of Treatment

A standard method of treatment of barbiturate poisoning was established and followed in all cases in the Queens General Hospital. This consisted of certain preliminary procedures common to all groups, the only variation in the treatment being the choice of coramine or picrotoxin.

Routine treatment:

1. A history was taken and physical examination was done, and an attempt made to identify the drug ingested. Wherever possible the prescription numbers were checked and the drug established. Members of the family were sent for to determine the amount of the drug in the patient's possession if known.

2. In all cases the stomach was aspirated with a large bore rubber tube, and washed with four to five liters of tap water, the organ being left empty. The washings were saved and sent either to our own hospital laboratory or to the Medical Examiners laboratory at Bellevue Hospital. The patients were then catheterized and the urine also sent for toxicological examination. (In all cases included in this report barbiturates were found either in the stomach contents or urine or both.)

3. An intravenous infusion of glucose and saline was started. Plasma was given to those in shock. The patient was put in a mild Trendelenberg position.

4. An airway was inserted where needed.

5. Bronchoscopy was done immediately wherever aspiration of food was suspected.

6. Frequent aspirations of the nasopharynx were done in comatose cases to maintain an unobstructed airway.

7. Either coramine or picrotoxin was used intravenously, using the infusion tubing as a ready means of entrance.

8. Nasal oxygen was used if need seemed evident.

9. Chemotherapy: Penicillin was employed, 50,000 units every three hours, intramuscularly, if temperature rose.

10. If the comatose condition persisted for several days, the nitrogen balance was considered and intravenous aminoacids, 70 gm. a day, were given. Vitamin therapy, thiamin chloride 5 mg., riboflavin 5 mg., nicotinic acid 50 mg., and vitamin C 100 mg. were given three times a day.

11. Nursing care is of great importance, with particular reference to turning the patient as a continual stimulant, to oral hygiene, to padding pressure points, to reduction of fever and to protecting against bullae.

Coramine Therapy

1. Routine procedure previously listed.

2. Five c.c. of 25 per cent coramine (10 c.c. in our latest cases) was given intravenously, followed by 5 c.c. every five minutes for the first hour. In addition, a constant amount was given by intravenous drip so that a base line amount of 5 c.c. per hour was administered. After the first hour, booster doses of 5 c.c. intravenously were given, on the hour. (This is important as the patients tend to relapse otherwise.) In more severe cases 5 c.c. were given every half hour by the clock, as boosters.

3. Therapy was continued until the patient had a return of reflexes, and moved spontaneously. (We now feel that this should be continued to the point of responding to stimuli such as answering questions, etc.)

Picrotoxin

1. A test dose of 3 mg. was given intravenously. If there was no reaction, 3 mg. was repeated every five minutes for three doses. After a 15

minute interval another series of three injections at five minute intervals was carried out. Therapy was continued thus until the return of reflexes and spontaneous motion. The patient was watched closely for dilating pupils and carried just to the point of muscle twitching. Sodium amytal was at hand in case of convulsions. In cases where coma was not deep a smaller dose was used as a follow-up with 3 mg. every 15 minutes.

Mixed (Coramine Plus Picrotoxin)

This consisted of the usual coramine routine plus a booster dose of picrotoxin, 3 mg. every 15 minutes.

These schedules were adhered to as closely as circumstances would allow.

Grading of Cases

All cases were graded as to severity in four groups in accordance with the criteria shown in table 1.

No case listed as grade 1 to 3 died regardless of the treatment, picrotoxin or coramine.

Table I

Grade	Conscious	Tendon Reflex	Corneal Reflex	Swallowing Reflex	Pupils	Coma
1	Yes	Yes	Yes	Yes	Normal	No
2	Semi	Yes	Yes	Yes	Constric.	No
3	No	Absent	Yes	Absent	Pinpoint	Yes
4	No	Absent	Absent*	Absent	Pinpoint	Deep

* The most important differential of a grade 3 from a grade 4 is the loss of the corneal reflex. This was found to be a sign of a poor prognosis.

A summary of the data in table 2 is given in table 3.

The extenuating circumstances should be considered in evaluating the above data, particularly the cases listed that entered the hospital in extremely serious condition and survived only a few hours. Examples: In 1945 list, Case 17, age 90; 1946 list, Cases 6 and 14, each in the hospital less than a day; also Case 7 (1946) with digestion of the bronchial tree and pneumonia.

Also note that one grade 4 case (No. 2, 1945 list) took only nine grains of a barbiturate, was treated with picrotoxin, and this drug was given credit for the successful result.

Case Reports

Case 1 (No. 3, 1945 list): This 55 year old white female was admitted an indefinite length of time after having ingested a large number of capsules of seconal. Physical examination on admission revealed a deeply comatose patient breathing slowly and quietly. The pupils were constricted and the eyes were slowly wandering. Corneal reflexes were absent. The chest showed moist rhonchi bilaterally. Heart and abdomen were normal. No abdominal reflexes were present. The extremities

were flaccid. All reflexes including biceps, triceps, patellar and ankle reflexes were absent. The patient was considered a grade 4 case. Urine was positive for barbiturate in large amount.

The usual supportive routine was given and picrotoxin was started. After 84 mg. of picrotoxin the patient had shown little response. The reflexes were still absent and the patient was still of grade 4 severity. Seven hours from the time of admission coramine was started and the patient showed a good reaction at once. The respirations increased, the reflexes returned, and after the administration of 21 c.c. of coramine, the patient was moving spontaneously. She went on to an uneventful recovery.

In this case we felt that picrotoxin was not improving the patient's condition and that only after the use of coramine was there a decided clinical improvement.

Case 2 (No. 18, 1945 list): This 43 year old white male was admitted after having taken an unknown amount of one of the barbiturates. He was deeply comatose on admission with complete areflexia, including absent corneal reflex. The pupils were small and a wandering motion of the eyes was present. The heart and chest were normal. The patient was considered a grade 4 case.

The routine supportive measures were carried out. Coramine was started. After 5 c.c. of coramine the patient reacted strongly with coughing, attempted vomiting,

TABLE II*

1945 Cases

No.	Age	Days in Hosp.	Dose Grains	Grade	Total Treatment	Response	Complication
1	28	6	18 N	2	6 mg. Pic.	Good	
2	63	6	9	4	42 Pic.	Good	
3	55	10	? Sec.	4	84 P, 21 c.c. C.	Fair	Slow
4	31	2	13½ Pent.	2	0	Good	
5	73	7	?	3	45 P.	Good	
6	25	6	?	3	24 P.	Good	
7	30	4	37 Ph.	2	2 C.	Good	
8	51	4	?	2	15 C.	Good	
9	46	2	18	3	120 P.	Fair	Convulsions
10	53	11	?	2	16 P.	Good	
11	30	2	12	2	15 P. 8 C.,	Good	
12	18	3	27 N.	2	15 P.	Good	
13	18	1	20 N.	2	0	Good	To psycho. hosp.
14	68	2	?	3	42 C., 12 P.	Good	
15	15	1	7½	1	0	Good	
16	29	3	70	2	0	Good	
17	90	1	Large	4	24 P., 50 C.	Death	Death
18	43	6	?	4	5 C.	Good	
19	12	1	12	2	22 C.	Good	
20	56	2	19 Sec.	2	18 P., 16 C.	Good	
21	26	6	?	1	0	Good	
22	40	3	?	2	6 P.	Good	
23	32	3	30 N.	2	3 P.	Good	
24	76	7	? N.	3	87 P.	Good	
25	37	2	12	2	0	Good	
26	28	1	25	2	0	Good	

* Code:
Pent.—Pentobarbital
N. —Nembutal
Sec. —Seconal
Ph. —Phenobarbital
O. —Supportive therapy only
Picrotoxin in mg.
Coramine in c.c.

TABLE II—*Continued*

1946 Cases

No.	Age	Days in Hosp.	Dose Grains	Grade	Total Treatment	Response	Complication
1	45	3	23	2	45 C.	Good	
2	38	4	?	4	17 C., 15 P.	Residual	To psycho. hosp.
3	27	3	12	1	0	Good	
4	32	14	36	3	188 C.	Good	
5	30	3	Large	4	151 C., 26 P.	Death	Death (aspiration pneumonia)
6	50	1	Large	4	6 C.	Death	Death (in hosp. 3 hrs.)
7	41	3	Large	4	141 C., 30 P.	Death	Death (aspiration pneumonia)
8	18	5	42	3	75 C.	Good	
9	53	4	Large	3	12 C.	Good	
10	42	12	?	2	52 C.	Good	
11	27	1	?	2	0	Good	
12	52	1	24	2	30 gr. Caf.	Good	
13	46	1	23	3	11 C.	Good	
14	48	1	45 N.	4	109 C.	Death	Extensive aspiration bronchopn.
15	36	1	43	2	3 C.	Good	
16	34	1	8	2	0	Good	
17	23	1	18	2	0	Good	
18	43	1	30	3	28 C.	Good	
19	69	1	8	2	12 C., 4 P.	Good	
20	35	1	12½	1	5 C.	Good	
21	38	1	?	2	11 C.	Good	
22	35	1	12	1	0	Good	
23	42	1	75	2	5 C.	Good	
24	32	1	30	2	3 C.	Good	
25	31	2	20	3	15 P.	Good	
26	15	1	7½	2	3 C.	Good	
27	50	1	26	1	0	Good	
28	30	1	4	1	0	Good	
29	50	2	27 N.	2	0	Good	
30	23	1	3	1	0	Good	
31	15	1	5	1	0	Good	
32	47	2	45 N.	4	137 C.	Death	

TABLE III

Grade	No. Cases	Treatment				Deaths	Deaths in Treatment Groups			
		Pic.	Cor.	Mix	Routine No Drug		Pic.	Cor.	Mix	Routine
1	9	0	1	0	8	0				
2	28	5	10	3	10	0				
3	11	5	5	1	0	0				
4	10	1	5	4	0	6	0	4	2	0
	58	11	21	8	18	6				

dilating pupils and spontaneous motions. No further coramine was given and the patient went on to recovery although he was somewhat drowsy for 24 hours.

Note: This was one of the best results with a small dose of coramine and illustrates the markedly individual character of the response. Large amounts of barbitures were recovered from the gastric washings and urine. At times there seemed

TABLE IV

Year	Cases	Deaths
1941	6	0
1942	15	2
1943	9	1
1944	11	0
1945	26	1
1946	32	5
	99	9 = 9.1%

to be no correlation between the grade of narcosis and the rapidity of the response to the analeptic.

Case 3 (No. 1, 1946 list): This 45 year old white male was admitted in a comatose state after having ingested 23 grains of seconal. He was assessed as a grade 3 case with peripheral reflexes absent but corneal reflexes present. The usual routine was followed plus coramine. The patient was conscious in two hours with a marked response to the initial dose of 10 c.c. of coramine. Only 22 c.c. in all were used.

Case 4 (No. 5, 1946 list): D. A., a 30 year old white female, was admitted in a comatose condition, at 10:00 p.m. on March 23. She had told friends a short time previously that she had taken a large number of nembutal capsules. Her stomach was promptly lavaged at another hospital and she was brought to the Queens General Hospital for treatment.

When first seen in the admitting department approximately 70 minutes after she had taken the barbiturate, and 20 minutes after completion of a gastric lavage she presented a picture of a deeply comatose patient with complete areflexia including absent corneal reflexes (grade 4). Blood pressure was 80 mm. Hg systolic and 0 mm. diastolic, pulse rate was 100, respirations were 24, and temperature was 99° F. The chest showed rhonchi, no dullness; heart sounds were good.

Picrotoxin treatment was instituted with the dosage and procedure outlined. The condition during the night changed but little except for occasional muscular twitching; the respirations became 35 a minute. Oxygen was given. At 3 a.m. corneal reflexes and tendon reflexes had returned, but by 8 a.m. they were absent again in spite of steady administration of picrotoxin. That evening (20 hours after treatment was begun) pulmonary edema was noted with full neck veins and rapid pulse. The knee jerks were slightly positive, the eyes wandering; some reaction was noted to the suction catheter in the pharynx. The temperature had risen to 102° F. White blood count was 40,200, 82 per cent polymorphonuclears; red blood count was 5.1 millions; hemoglobin was 14.5 gm. The CO_2 combining power was 46 vol. per cent, urea nitrogen 47 mg. per cent, creatinine 2.6 mg./100 c.c. Penicillin, 30,000 units every three hours, was begun intramuscularly.

On the morning of March 25 her condition was approximately the same and coramine was begun, the picrotoxin being continued. In four hours there seemed to be a change for the better; she now moved her head and her lips, her reflexes had returned, the pupils were small; she was vomiting yellow fluid. That evening the temperature rose to 103.5° F., and at 1 a.m. she suddenly became worse. Her face was brownish, respirations were rapid, pulse rate was 190, heart sounds were fair, restlessness was pronounced, pupils were dilated and divergent.

At 9 a.m., March 26, 1946, she was suffering from peripheral vascular collapse. Blood pressure was 0/0, skin was pale and moist, respirations were shallow and gasping, pupils were widely dilated, heart was rapid, and sounds were of poor quality. Chest showed dullness in the right lower lobe. The reflexes were active. There was a sudden cessation of breathing with the heart beating five minutes longer.

This grade 4 case shows combined therapy with fatal result, death being due to pneumonia. An autopsy revealed patchy bronchopneumonia plus moderate cerebral edema.

Case 5 (No. 6, 1946 list): A 50 year old white female was admitted approximately 12 hours after she took an unknown amount of barbiturate. Her past history was irrelevant except for a diagnosis of pernicious anemia with no therapy for months.

She was considered a grade 4 case. The temperature was 101° F., pulse 130, respirations 32, blood pressure 90 mm. Hg systolic and 50 mm. diastolic, skin of yellowish tint. The chest showed many moist bubbling râles; heart sounds were faint. The liver was two fingers'-breadth below the costal margin and a question of liver nodules was raised. Spinal tap showed pressure 230 mm. of water, with normal dynamics. Blood chemistry: blood sugar 18 mg./100 c.c., CO_2 58 vol. per cent. Urine: albumin 2+; large amounts of barbiturate were found. Blood smear was typical of pernicious anemia. Roentgenogram: The right and left upper lobes suggestive of pneumonia with atelectasis.

The diagnosis was not considered barbiturate poisoning for several hours after admission to the hospital and as a result treatment was delayed. The patient died three hours after admission.

The therapy was both late and insufficient. At necropsy, the death was considered to be due to pneumonia and pernicious anemia. This case was listed as a coramine failure, although obviously her condition was terminal on admission.

Case 6 (No. 7, 1946 list): R. M., 41 year old white male, was admitted to the hospital February 13, 1946 in a deeply comatose state, after having been found unconscious on the floor with red and blue capsules nearby (thought to be Tuinal).

Areflexia, marked cyanosis, shallow respirations, fixed small pupils were found on examination, and the patient was vomiting. Dullness to percussion was found in the right middle and lower lobes of the lungs with absent breath sounds over these areas. The heart sounds were rapid and of poor quality. The case was considered of grade 4 severity.

Bronchoscopic aspiration shortly after admission revealed large amounts of peas and carrots, withdrawn from the pharynx and trachea. Breath sounds returned to portions of the right lung after aspiration but flatness continued at the base.

Treatment was instituted as outlined, 5 c.c. of coramine were given intravenously every five minutes, and an intratracheal catheter was passed. The condition seemed to improve with full respiration and an increase in heart sounds. After two hours of treatment, owing to an error in interpretation of orders, the dosage of coramine given was reduced to 5 c.c. every hour instead of every five minutes. A total of 28 c.c. of coramine had been given in the first two hours.

On February 14, 1946, the patient was moving about in bed, comatose, with a return of corneal reflexes only. The pulse was weak, rapid and the color of the skin cyanosed. Large amounts of brown fluid continued to be aspirated from the tracheal tube. Blood pressure was 0/0. A Levine tube was in the stomach with continual suction; an airway was in place. Roentgenogram of the lungs showed extensive patchy atelectasis and bronchopneumonia. Bronchoscopic examination revealed tarry material beyond the reach of the bronchoscope. During the afternoon, the reflexes became hyperactive and the pupils dilated. The patient was unconscious. A total of 28 c.c. of coramine was given in this 24 hour period.

On February 15, 1946 the patient's condition was poor, with temperature about 102° F.; the total serum protein was 4.2 gm./100 c.c., urine was normal, leukocytes numbered 5,500 with 72 per cent polymorphonuclears, 14 gm. of hemoglobin, and 5.7 million red blood cells. Picrotoxin, 7.5 mg., was given intravenously this day without response. The next day the temperature was higher and a return was made to coramine therapy, 3 c.c. every hour intravenously. Booster doses of 10 to 15 c.c. were given several times during the day. Although the semicoma continued, the patient moved spontaneously. Penicillin, 25,000 units every three hours intramuscularly, together with thiamine chloride and niacin, was administered. The con-

dition became worse and the patient died four days after admission, with a temperature of 103° F. rectally.

At necropsy the findings were essentially those of necrosis of the entire tracheobronchial tree with digestion of the mucosa. The lungs showed grayish-green necrosis with small abscess formation in the right middle and lower lobes, and the left lower lobe. The pathologist's diagnosis included digestion of the bronchial tree and pneumonia as the causes of death.

This illustrates a grade 4 case, treated almost entirely with coramine, only a small amount of picrotoxin being used, without recovery, death being due to pulmonary complications.

Discussion

In the years 1945 and 1946 there was a marked increase in the number of cases of barbital poisoning and in the number of deaths, as compared with the previous three years. Some physicians maintain that most patients suffering from barbital poisoning will eventually recover with supportive treatment and with the aid of stimulants of less potency than coramine or picrotoxin. Careful analysis of statistics proves that this is not the case. Some hastily compiled figures seem to show better results from the least strenuous treatment. This illustrates how statistics alone can mislead when taken without analysis of the background factors, particularly without grading the depth of the narcosis, aspiration, etc.

Self-medication is the main etiological factor in poisoning. In many cases, the poisoning is intended as suicide; others develop a dependence on the barbiturate and take it in too large doses. Richards [17] has discussed the peculiar condition known as "automatism" in which an individual having become accustomed to the use of the drugs may fail to have deep sleep develop. In this twilight zone, the individual does not exhibit normal inhibition and reason, and mechanically (automatically) takes all of the remaining tablets.

There has been a marked increase in cases of self-medication. The grade 4 group have taken enormous quantities of drugs, judging from the amount recovered in the urine and as determined by careful histories. It has been our finding that very few grade 4 cases were found in the first three years of this survey as compared with the last two years. This again simply reflects the increasing amounts of barbiturates being dispensed and therefore available. The recent attempts to class barbiturates with narcotics under the law is not the entire answer, as in all of the cases of grade 4 narcosis investigated, the drugs were obtained with a physician's prescription. Most of these people went to several doctors and obtained prescriptions from each for from 12 to 50 capsules. Some of the patients had as many as 15 bottles from as many doctors.

There has also been a swing away from the use of long acting members of the barbiturate group, such as barbital and phenobarbital, to the shorter and quicker acting members, notably nembutal and seconal. In our experience the latter group have been more lethal, weight for weight. Tatum [3]

feels that all of the barbiturates, except barbital and phenobarbital, have a short induction period.

Prolonged depression from the ingestion of these drugs results in complications of a serious nature, namely pneumonia, pulmonary edema, cerebral edema, prolonged hypoxia, nutritional deficiencies, depressed kidney function, decubitus ulcers and transient or more permanent neurological sequelae.

Analeptic treatment should be instituted as soon as possible and carried on with a definite plan adapted to needed intensity and duration. It is our feeling that where coramine has been used with unsatisfactory results in the past, in many instances better effects would have been obtained with a schedule of larger doses.

In no case where coramine failed did picrotoxin succeed in saving the patient. In several cases where picrotoxin did not help, coramine gave good results.

In several cases picrotoxin caused severe convulsions, some requiring the administration of sodium amytal for control. In no case did coramine cause convulsions. Coramine is safer to use for this reason and can be given by nurses without danger, whereas picrotoxin must be given with a physician on hand at all times because of the danger of convulsions.

Review of the statistics shows that every fatal case was in group 4. No cases listed in groups 1 to 3 died. The main difference between group 3 and group 4 is the loss of the corneal reflex. Therefore, when the corneal reflex is lost, the prognosis becomes much more grave. Sixty per cent of those with absent corneal reflex died.

The early aspiration of the stomach with immediate therapy is of prime importance. Nothing is to be lost and much is to be gained by prompt action. Even if the type of the depressant is not known, this does not change the method of treatment.

Therapy should be maintained until the patient moves spontaneously and has a return of all reflexes. It is better to continue therapy to the point of reaction, at which time the patient responds to mild stimuli.

The study and comparison of these drugs is being continued in the Queens General Hospital, this being a preliminary report. We wish to focus more attention on the value of coramine and to stress the safety of much larger doses than are usually given. Our doses are to be increased in future cases to 10 c.c. of coramine every five minutes intravenously until the patient reacts, and large doses are to be continued for some time.

Summary and Conclusions

The therapy of barbiturate intoxication is an increasingly important problem confronting the medical profession. Treatment is discussed comparing coramine (Nikethamide) with picrotoxin. The study suggests further recognition and use of coramine as a relatively non-toxic, effective analeptic agent in the treatment of barbiturate intoxication.

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SKELETAL LESIONS IN HODGKIN'S DISEASE*

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The skeletal lesions of Hodgkin's disease are well recognized as numerous reports in the literature indicate. Steiner mentions in his Review [1] in 1943, having found in the Index Medicus and Quarterly Cumulative Index Medicus 1922 to 1942, approximately 92 titles of papers dealing primarily with skeletal changes. In spite of this accumulated information there are many gaps in our knowledge of the mechanism of these granulomatous lesions in the skeleton. In particular, we lack exact knowledge as to the mode of spread in the skeleton, the frequency, and the inception of the lesions, with reference to the onset of the primary disease.

It was formerly believed that Hodgkin's lymphogranuloma spread only through lymphatic tissue. At present the conception that the lesions of Hodgkin's disease may also spread through the reticuloendothelial system appears to be quite well established. Some investigators believe this disease should be considered as a disease of the reticuloendothelial system.[2]

There appears to be quite general agreement among investigators of Hodgkin's disease that skeletal involvement means marrow involvement. The actual mechanism of marrow involvement has not been adequately demonstrated. Three methods are commonly mentioned, direct invasion from adjoining granulomatous lesions, usually lymph nodes, hematogenous invasion through small lymphogranulomatous emboli, or transference of an agent capable of initiating a focus in situ. This latter method could also initiate a lesion primary in the bone marrow, bearing in mind, of course, that the etiology of Hodgkin's disease is at present unknown. Several authors have reported cases where the first clinical evidence of the disease was demonstrated in the skeleton.[3]

In the reported cases of skeletal involvement the lesions described have usually been either osteolytic (destructive) (figure 1), osteoplastic (proliferative) (figure 2) or periosteal (infiltrative) (figure 1). There are various combinations of either two or even three of the above types shown in a single skeletal lesion (figure 1).

With respect to the study of aspirated bone marrow as a means of investigating skeletal lesions in the living patient with Hodgkin's disease, it should be stated that this method is considered of little practical value by most investigators of this disease. Since 1938, we have studied the aspirated sternal marrows from 59 patients with Hodgkin's disease in order to ac-

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cumulate data, which we considered might suggest bone marrow invasion with the lesions of Hodgkin's lymphogranuloma. It was recognized that a specimen of aspirated sternal marrow would probably not contain material from an actual lesion of lymphogranuloma, except by the mere element of chance. We were searching for a cellular pattern in the aspirated specimens

FIG. 1. Combined osteolytic and periosteal lesion of femur.

of marrow that might indicate, relatively early, whether other portions of the skeletal marrow had become involved by the typical lesion of Hodgkin's granuloma. It was our hope that certain abnormal changes in the cell pattern might be demonstrated in aspirated sternal marrow from patients with Hodgkin's disease, and that these changes might be found to indicate a

functional disturbance of hematopoiesis due to granulomatous invasion of a portion of the marrow.

Source of Material and Methods

Material for this study was obtained from the hematologic clinic, the hospital and the department of pathology of the University of California Medical School. Twenty cases of Hodgkin's disease proved by autopsy were investigated for evidence of marrow involvement. The specimens of marrow studied were the usual routine specimens taken at autopsy either from the sternum or from a rib. In a few instances material was obtained from an

Fig. 2. Proliferative lesions of ilia.

actual skeletal lesion and in addition to Zenker-fixed material, spreads were made directly on glass slides and the film stained by Wright's, counterstained by Giemsa's stain. Aspirated sternal marrows were studied from 12 of these 20 patients during life. Forty-seven patients in whom the diagnosis was confirmed by surgical biopsy of an enlarged lymph node, were subjected to one or more sternal marrow aspirations in the hematologic clinic. This group of patients also had some type of roentgenologic investigation for evidence of skeletal lesions.

The technic used for study of aspirated bone marrow was the following: 1 c.c. of sternal marrow was drawn into a 5 c.c. luer syringe and immediately discharged into a centrifuge tube in which a few particles of heparin had been placed. This material was centrifuged for five minutes at approxi-

mately 2000 r.p.m. The serum and fat were withdrawn and discarded, and from the lighter colored, myeloid layer, material was transferred to a cover glass on which films were drawn by superimposing two cover glasses. After using this method for approximately one year we changed to the practice of withdrawing approximately 0.2 to 0.3 c.c. of sternal marrow into the aspirating needle and attached syringe, and transferring this material directly to the cover slips. We found our best preparations were made by withdrawing the plunger of the 5 c.c. luer syringe and attempting to pick out small pieces of marrow from the syringe by means of a capillary pipette.

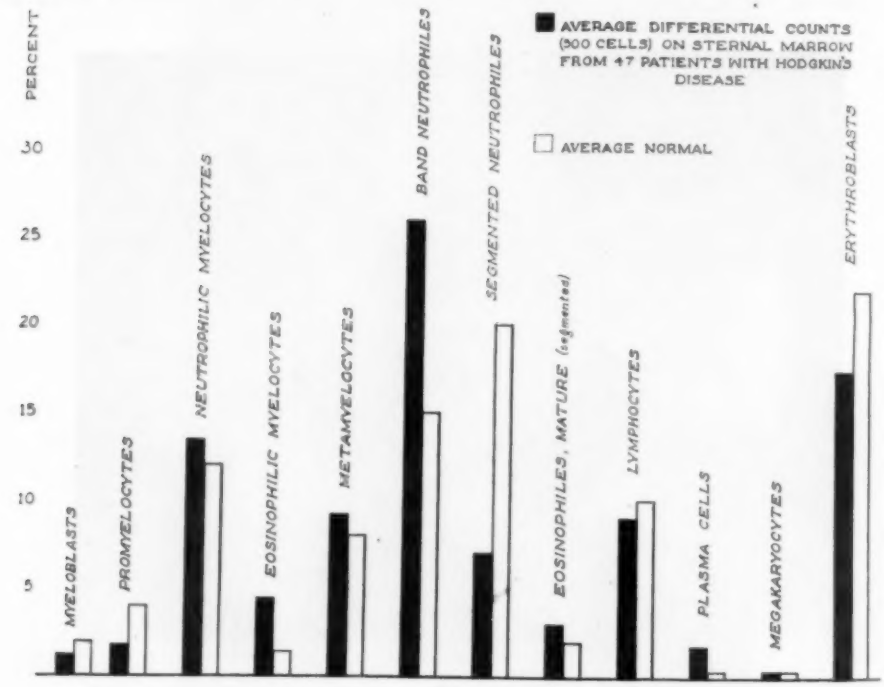

FIG. 3.

The remaining clotted portion of marrow was next removed from the syringe and placed in Zenker's solution for fixed-tissue preparations to be studied later. This method was used up until the time of completion of the present study. The marrow specimens were examined and the cells counted by both authors, each counting 500 cells.

RESULTS FROM ASPIRATED AND AUTOPSY MARROW INVESTIGATION

Figure 3 shows a "shift to the left" of the myelocytic elements. Of these elements the neutrophilic myelocytes showed a moderate increase, the eosinophilic myelocytes a marked increase, neutrophilic band cells dis-

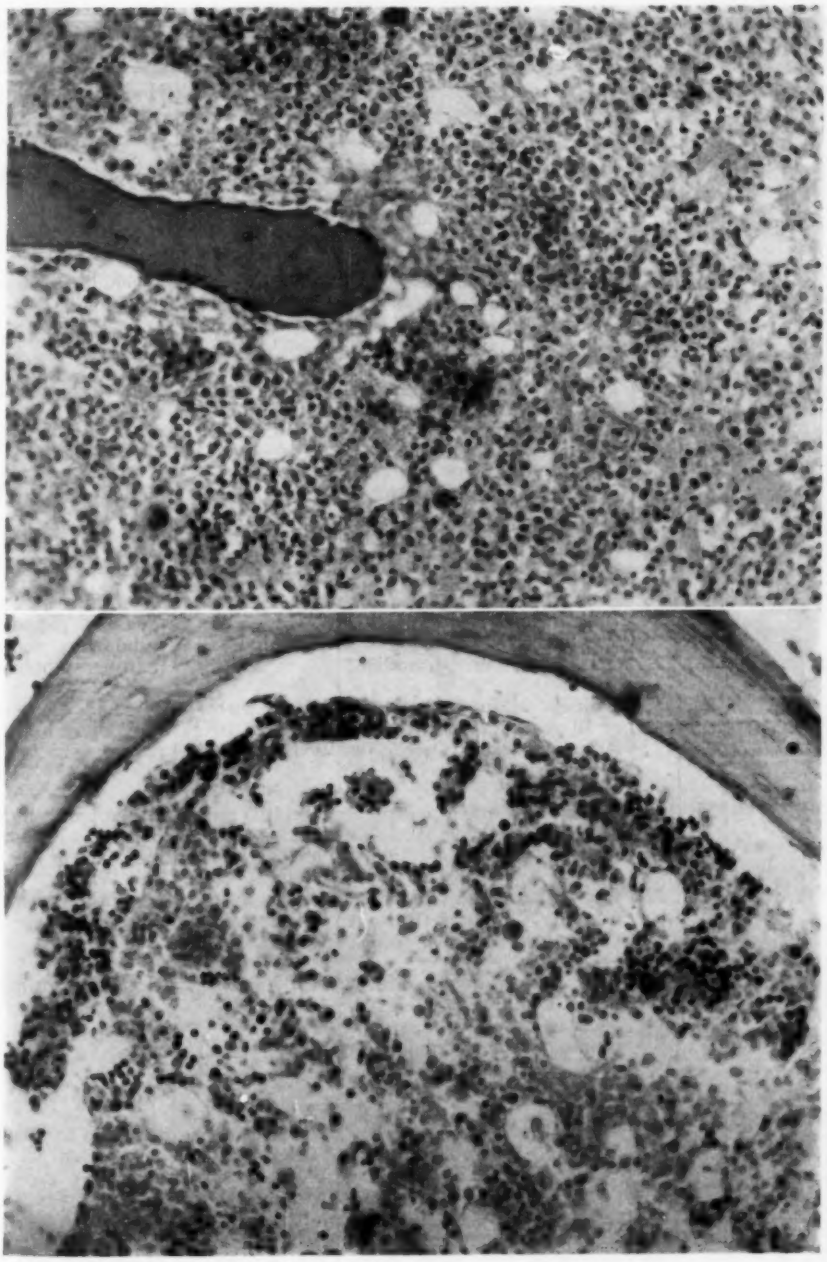

FIG. 4a (*Above*). Typical lymphogranulomatous lesion of marrow.

FIG. 4b (*Below*). Replacement of normal marrow tissue by Hodgkin's lymphogranuloma.

TABLE I

No.	Patient	Sex	Age	Clinical Manifestations	Blood Findings	Bone Marrow (Autopsy)
1	C. W.	M.	57	Chills and fever of three months' duration.	Hb. 8 gm. R.B.C. 2.5 W.B.C. 2,200	Hodgkin's granuloma
2	S. S.	M.	51	Three year history of lymphadenopathy, fever, anorexia, weakness and weight loss.	Hb. 5.5 gm. R.B.C. 2.55 W.B.C. 2,800	Hodgkin's granuloma
3	R. O.	M.	31	Obstructive jaundice. True nature of disease disclosed by operation for jaundice.	Hb. 10.4 gm. R.B.C. 3.43 W.B.C. 16,500	Myelofibrosis and eosinophilia
4	S. A. S.	M.	30	Three and one-half year history of weakness, dyspnea, abdominal discomfort. Enlarged cervical lymph nodes.	Hb. 6 gm. R.B.C. 3.1 W.B.C. 19,000	Myeloid hyperplasia
5	J. S.	F.	21	Fever, weakness, weight loss, cough and dyspnea of 15 months' duration. Enlarged nodes, left axilla.	Hb. 12 gm. R.B.C. 4.09 W.B.C. 22,800	Hodgkin's granuloma
6	C. B.	M.	42	High intermittent fever for 10 months. Generalized adenopathy. Enlarged spleen and liver. Jaundice.	Hb. 6 gm. R.B.C. 2.13 W.B.C. 1,850	Myelofibrosis with areas of pleomorphic cellularity, including many eosinophiles
7	E. E.	F.	52	Painless abdominal tumor of 10 years' duration. Enlarged thyroid. Osteolytic lesions, ribs.	Hb. 12.8 gm. R.B.C. 4.10 W.B.C. 4,800	Myeloid and megakaryocytic hyperplasia
8	P. C.	M.	36	Generalized adenopathy. Dyspnea and cough.	Hb. 12.5 gm. R.B.C. 4.44 W.B.C. 5,650	Eosinophilic hyperplasia, fibrosis, many megakaryocytes
9	W. M.	M.	27	Cervical and axillary adenopathy. Pleural effusion. Osteoplastic lesions, pelvis.	Hb. 8 gm. R.B.C. 2.73 W.B.C. 19,000	Hodgkin's granuloma
10	A. B.	M.	25	Illness of seven years' duration, manifested by fever, weakness, weight loss, abdominal pain, lymphadenopathy, splenomegaly and hepatomegaly.	Hb. 7 gm. R.B.C. 3.82	Hodgkin's granuloma
11	A. H.	F.	46	Generalized lymphadenopathy and splenomegaly.	Hb. 10 gm. R.B.C. 2.82 W.B.C. 44,250 with marked left shift.	Myeloid hyperplasia
12	J. B.	F.	18	Illness of five years' duration, severe bone pains at onset, left shoulder. Later, pains in hips, legs and back. Cervical and inguinal adenopathy one year after onset.	Hb. 3.5 gm. R.B.C. 1.00 W.B.C. 4,000	Hodgkin's granuloma

TABLE I—*Continued*

No.	Patient	Sex	Age	Clinical Manifestations	Blood Findings	Bone Marrow (Autopsy)
13	W. S.	M.	49	Lymphadenopathy, weakness, weight loss and splenomegaly. Symptoms five years' duration.	Hb. 6.9 gm. R.B.C. 3.15 W.B.C. 12,000	Hodgkin's granuloma
14	A. McD.	M.	33	Back pain and sciatic syndrome of one year's duration. Osteolytic lesions, spine.	Hb. 7 gm. R.B.C. 3.05 W.B.C. 4,000	Hodgkin's granuloma
15	J. F. L.	M.	30	Lumbar pain followed by hypesthesia of low back and paraplegia. Osteolytic lesions L3, 4. Six years' duration since onset of first symptoms.	Hb. 9.5 gm. R.B.C. 3.8 W.B.C. 4,400	Hodgkin's granuloma
16	J. L.	M.	24	Symptoms of two years' duration. Primarily those of mediastinal pressure with superior vena cava block. Pleural effusion.	Hb. 12 gm. R.B.C. 5.02	Fibrosis with eosinophilia
17	F. S.	F.	44	Dysphagia and pain in left upper quadrant for eight years. Enlarged nodes in neck. Osteolytic lesions, pelvis.	Hb. 8.8 gm. R.B.C. 2.8 W.B.C. 2,400	Hypoplastic
18	J. M.	M.	51	Intermittent abdominal pain for three months. Splenomegaly and abdominal mass.	Hb. 8 gm. R.B.C. 2.82 W.B.C. 26,500	Myeloid and megakaryocytic hyperplasia
19	W. S.	M.	27	Swelling in neck for two years and six months. Pain in right hip and low back for six months. Osteoplastic lesions, pelvis.	Hb. 7 gm. R.B.C. 2.71 W.B.C. 2,200	Hodgkin's granuloma
20	R. M. E.	F.	48	Swelling left upper quadrant five years. Pain left shoulder four weeks. Splenomegaly and hepatomegaly. Osteolytic process left humerus and scapula.	Hb. 7 gm. R.B.C. 2.75 W.B.C. 13,200	Hodgkin's sarcoma

played a marked increase, and segmented eosinophiles a moderate increase. Neutrophilic metamyelocytes were moderately increased and the plasma cells showed a well marked increase. A breakdown of these differential counts by grouping patients according to duration and distribution of their disease showed a sharp rise in per cent of myeloblasts, promyelocytes, neutrophilic and eosinophilic myelocytes, and plasma cells, in the group with longest duration, and widest distribution of disease. In at least three of these patients the marrow cell counts suggested a myelocytic leukemoid reaction. We found in those marrows where aspiration achieved satisfactory specimens, i.e., with small particles of marrow in the aspirate, a considerable

number of immature myelocytic elements with a marked increase of eosinophilic myelocytes.

Table 1 shows the results of bone marrow study of fixed-tissue preparations in 20 cases of Hodgkin's disease in whom autopsies were performed. Typical granulomatous lesions as illustrated in figures 4a, 4b, were found in the marrows of 11 patients. In four other cases the marrow disclosed the picture of a leukemic infiltration with a preponderance of neutrophilic and eosinophilic myelocytes. Table 1 discloses peripheral blood findings of a well marked leukocytosis in three of these cases; in one instance a leukocytic count of 44,200 was present. The aspirated sternal marrow in 12 of these patients was examined during life and in each instance disclosed a marked shift to the left, with a high per cent of neutrophilic and eosinophilic myelocytes.

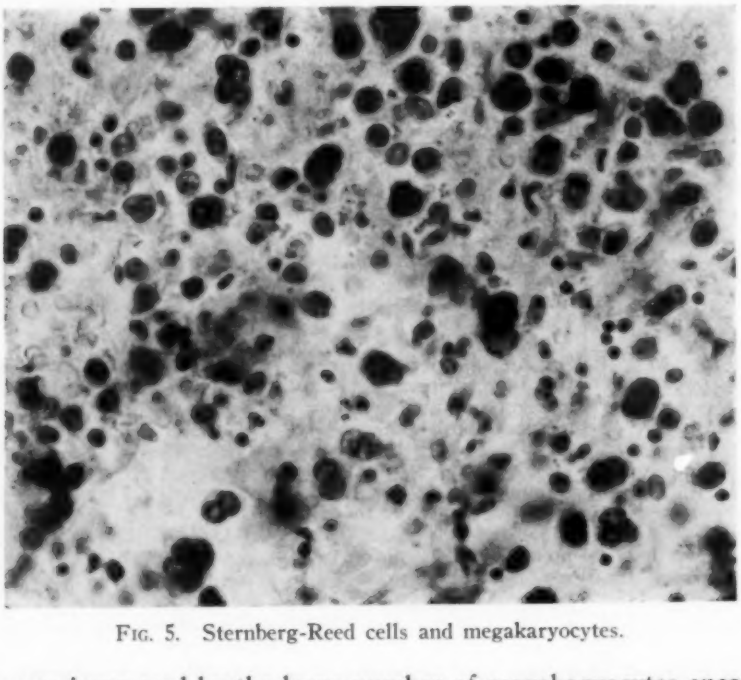

FIG. 5. Sternberg-Reed cells and megakaryocytes.

We were impressed by the large number of megakaryocytes encountered in some of the preparations (figure 5). In order to determine the significance of this observation, particularly as megakaryocytes in Hodgkin's disease have frequently been studied and commented on by other investigators, we did a series of counts on the marrows of 18 autopsy cases and 49 living patients. The method used was to count 100 fields with a high-dry lens. Normals used for control showed an average of 20 megakaryocytes per high-dry field. Forty-nine patients in various stages of Hodgkin's disease showed an average of 25.5; the fixed tissue preparations of 18 autopsy patients showed an average of 78 per 100 high dry fields. One patient whose counts

were not included showed 414 megakaryocytes per 100 high dry fields. This patient showed a marked anemia, her marrow revealing much fibrosis in addition to many megakaryocytes and areas of Hodgkin's granuloma. This patient's marrow corresponds to a type of Hodgkin's disease described by Rhoads [4] in connection with studies on aplastic anemia, and designated refractory anemia with megakaryocytic marrow.

Incidence of Skeletal Lesions

Table 2 shows the incidence of skeletal lesions in Hodgkin's disease as determined by various investigators. Two types of investigation are recorded in the statistics of this table: namely roentgenologic and post mortem.

Table II

Statistics of Various Authors Showing Incidence of Skeletal Lesions in Hodgkin's Disease

Authors	Total No. of Pts.	Number with Bone Lesion	Percentage of Incidence	Method of Study
Dresser and Spencer	149	16	10.7	Roentgenologic
Vieta, Friedell and Craver	257	38	14.8	Roentgenologic
Vieta, Friedell and Craver	47	23	49.0	Necropsy
Craver and Copeland	172	27	15.7	Roentgenologic
Uehlinger	50	15	30.0	Necropsy
Stephani	70	28	40.0	Necropsy
Schenk	107	8	7.5	Roentgenologic
Werthman	12	8	66.0	Necropsy
Authors	20	11	55.0	Necropsy
Authors	65	17	26.0	Roentgenologic

A comparison of these percentages derived from the two types of study indicate that roentgenologic statistics may be misleading unless the limitations of this method of study are kept in mind. Roentgenologic bone surveys must be carried out on all patients studied and roentgenograms carefully searched for skeletal lesions in order to obtain the true statistical incidence. Critical study of postmortem marrow investigations reveals a similar type of statistical error. This point is well illustrated by the postmortem studies of Steiner in 1943.[1] He secured specimens from different portions of the skeleton (three to nine bones) in 14 consecutive cases of Hodgkin's disease; marrow sections from 62 bones disclosed granulomatous lesions in 38 of 62 sections or a per cent of 61.2. In three cases examined every section showed the presence of Hodgkin's lymphogranuloma. In each of three cases which showed no involvement, only three different bones were examined. It is quite apparent that more extensive and particularly more carefully planned studies in connection with both types of investigation will reveal a higher incidence of skeletal involvement than the figures recorded up to the present.

Origin and Spread of Marrow Lesions

Skeletal lesions are practically synonymous with marrow lesions; the focus originating in the bone marrow and enlarging until it erodes the con-

tiguous cortex of the bone. Occasionally instances are encountered where the granuloma appears to invade the bone from without, entering through the periosteum from contiguous lymphogranulomatous tissue. It is our impression that when this occurs the disease is widespread and fairly well advanced. Our interest has centered on the question of how early in the course of the disease does bone marrow involvement occur? A fairly large number of our cases appeared to have marrow involvement relatively early in the course of their disease. One method of obtaining direct proof of this possible involvement would be multiple samplings of the red marrow sites in the skeleton by means of surgical biopsy. This is scarcely feasible in the living patient so that it becomes necessary to use indirect methods such as study of aspirated marrow specimens.

It seems reasonable to assume that the marrow and the spleen because of their histological structure may be quite as favorable sites for early proliferation of Hodgkin's lymphogranuloma as lymph nodes. Both marrow and splenic tissue have labile growth potentialities in their cellular components, and their filter propensities with stasis of blood in the sinusoids, might readily harbor the agent responsible for proliferation of lymphogranulomatous lesions. This idea might well be objected to on the ground of its being purely theoretical, yet it constitutes an approach to the study of the spread of marrow lesions, albeit not an easy approach. There are lesions described in the literature [5] where the spleen and bone marrow have been involved with Hodgkin's granuloma before recognizable involvement of lymph nodes has occurred. Two patients of our series are herewith briefly reported as illustrating this point.

Case 1, an Italian girl, aged 14, became ill in March, 1937, with pain over the left scapular region. Pain was severe enough to interfere with sleep. About two months after onset, the pain shifted to the right knee, then after one month it involved the left knee as well. Pain interfered somewhat with walking, but the knee-joints proper were not swollen nor sore. In December, 1937, she had to stop school because of pain over both lower quadrants of the abdomen and over the low back. After a few weeks pain extended to involve the left hip and she walked with a limp. In January, 1938, a few tender "lumps" appeared in the left side of the neck. During January and February, 1938, patient remained in bed. During this time a "dribbling" of urine appeared. By April of 1938 the patient was having difficulty in sitting upright in bed; she was scarcely able to walk, so on April 29, 1938, she was admitted to the University of California Hospital. The pertinent findings at this time were: A few slightly enlarged palpable lymph nodes in the posterior triangles of the neck. Blood count, hemoglobin 70 per cent; red blood cells 3.70 millions; white blood cells 16,900; neutrophiles 84; filaments 39; non-filaments 45; lymphocytes 15; monocytes 1 per cent; blood serum calcium 11.8 mg. per cent; phosphorus 6.1 mg. per cent. Biopsy of a cervical lymph node was reported; lymphoma, probably Hodgkin's disease. Roentgenograms showed: osteolytic lesions in the distal extremities of both femora (figure 6), proximal ends of both tibiae and fibulae, collapse of ninth thoracic vertebra (figure 7), involvement of both wings of the ilia with areas in both ischii (figure 8) and head of left humerus. The patient was started on roentgen therapy with some improvement but as the diagnosis of Hodgkin's disease was questioned by the roentgenologist administering the treatment, a surgical biopsy of the right iliac crest was

performed. The fixed tissue marrow specimens were diagnosed as Hodgkin's disease. Roentgen therapy was continued; also a limited course of therapy with the radioactive isotopes of strontium and phosphorus was administered. After entry into the hospital her anemia became progressive, necessitating multiple transfusions. In De-

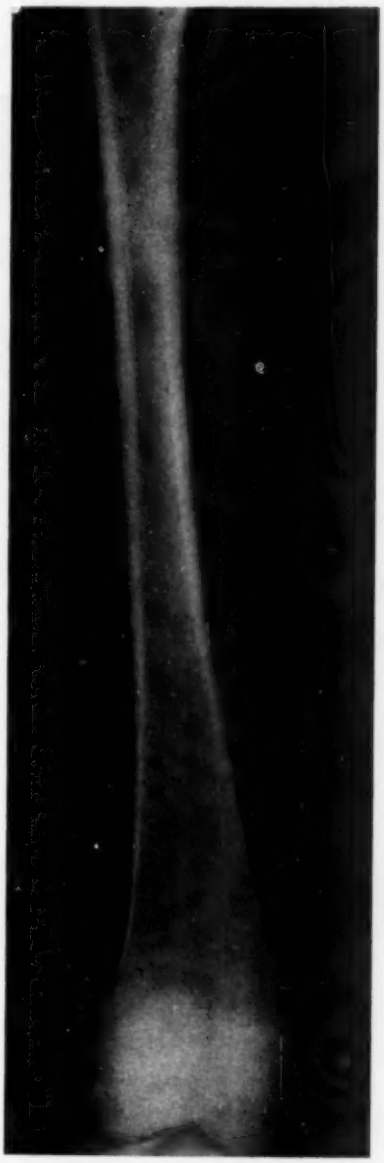

FIG. 6. Case 1. Osteolytic lesion distal portion femur.

cember, 1940, the skull showed osteolytic lesions by roentgenologic examination. On September 7, 1941, she entered the hospital for further transfusions. By this time her anemia was extreme, the hemoglobin was 18 per cent; red blood cells 900 thousand;

white blood cells 4,000, neutrophiles 61; filaments 35, non-filaments 26; lymphocytes 26; monocytes 13. After five transfusions she recovered sufficiently to leave the hospital, returning on April 29, 1942, at which time death occurred, exactly four years after her first hospital entry and five years after her first symptoms were noted. At necropsy the marrow was found to be extensively invaded and crowded out by lymphogranulomatous lesions with areas of new marrow formation in the fatty portions of the long bones. The history indicates that the first involvement of superficial

FIG. 7. Case 1. Collapse of ninth thoracic vertebra.

lymph nodes was noted 10 months after symptoms of skeletal involvement appeared.

Case 2. A single female, aged 44, was referred to one of the authors (E. H. F.), March 11, 1947, because of severe anemia which did not respond to therapy with either parenteral liver extract, folic acid or iron by mouth. Examination revealed a pale, slightly icteric woman with a very large spleen which extended well into the pelvis. Laboratory studies indicated a severe hemolytic anemia, and splenectomy was advised. On March 20, 1947, Dr. Frederick Foote removed the patient's spleen at the Franklin

Hospital. At operation four nodules about 2.5 cm. in diameter were noted in the tissues of the splenic pedicle. One of these nodules was pale yellow in color and firm in consistency, while the other three were bluish in color, resembling splenic tissue. The yellowish nodule was removed and a frozen section prepared for emergency diagnosis, which was reported as typical of Hodgkin's disease. The spleen along with the three accessory nodules was removed. Exploration of the abdomen failed to reveal any other nodes or evidences of spread of Hodgkin's lymphogranuloma. The spleen weighed approximately 1500 grams and a section showed whitish yellow nodules varying from a millimeter to about 2 cm. in diameter. Fixed tissue sections of the spleen showed microscopically the lesion of Hodgkin's disease. The patient made an uneventful recovery from her operation, and with the aid of transfusions (6 liters of blood) the blood count slowly returned to normal after approximately three months in the hospital.

FIG. 8. Case 1. Lesions of ilia and ischii.

After about three months spent at home, during which time she was comfortable and felt quite well, pain appeared over the lower spine. Patient's home was some distance from San Francisco; therefore she had been requested to return to the hospital in the event of symptoms recurring. On October 7, 1947, at reëntry, a chest film and roentgenograms of the spine were made. These were negative with the exception of increased density in the fourth lumbar vertebra. Roentgen therapy was given over the spine with relief of pain after six treatments. On November 11, 1947, approximately one month later, the patient returned, complaining of pain over the thoracic spine and left chest. Roentgenograms of the spine now showed a compression fracture of the twelfth thoracic spine (figure 9). On November 26, 1947, a bone survey showed a destructive lesion at the medial end of the left clavicle (figure 10), also an

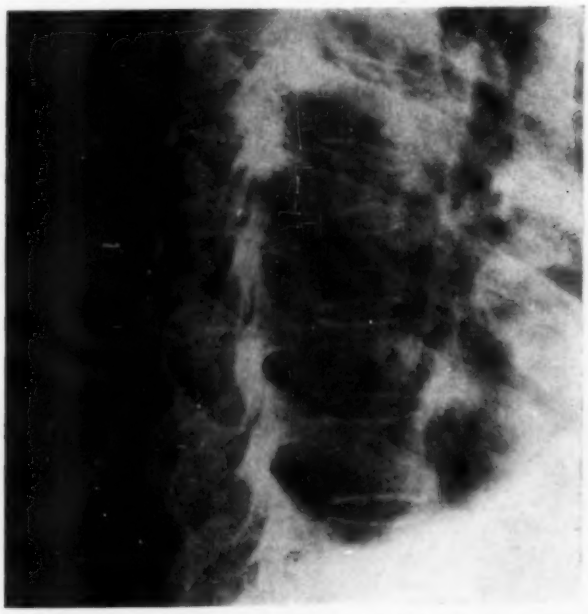

FIG. 9. Case 2. Compression fracture twelfth thoracic vertebra.

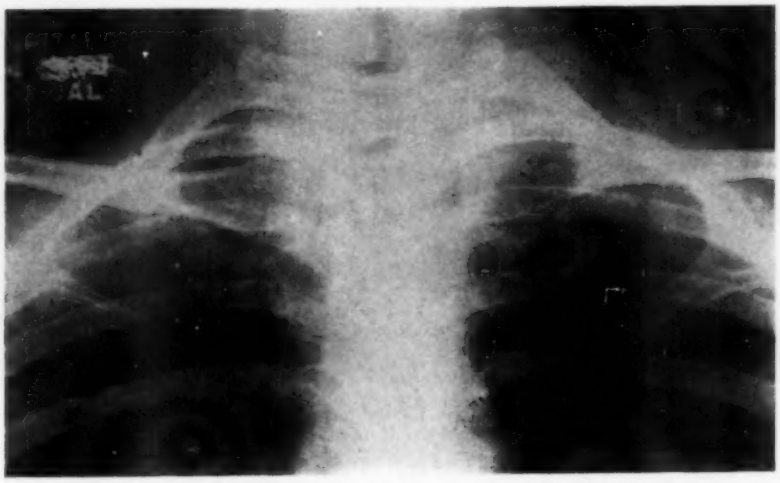

FIG. 10. Case 2. Destructive lesion medial end left clavicle.

osteolytic lesion of the ascending ramus of the right ischium and a portion of the acetabulum. Roentgen therapy was carried out in an attempt to alleviate pain and prevent the spread of her lymphogranulomatous lesions. On January 29, 1948, films showed new destructive lesions involving the fifth and sixth thoracic vertebrae and the second right rib at the axillary line. On March 11, 1948, films disclosed osteolytic lesions throughout the shaft of the middle portion of the left femur (figure 11). The bones of the pelvis were now intact following roentgen therapy. By April 8, 1948 further roentgenograms showed compression fractures of the first and second lumbar

FIG. 11. Case 2. Osteolytic lesions middle portion left femur.

vertebrae, healed, recalcified fractures of the second and fifth right ribs and recent spontaneous fractures of the tenth and eleventh ribs, left, in the anterior axillary line.

A notation in the patient's record states that on December 15, 1947, she noted enlarging lymph nodes on the right side of the neck in the anterior and posterior cervical triangles. This was approximately 10 months after our first examination. The appearance of enlarging superficial lymph nodes was carefully watched for and checked, as we were anxious to ascertain the time relation of the first definite evidence of lymph node involvement in relation to the onset of skeletal lesions. On November 11, 1947 there was roentgenologic evidence of skeletal involvement in rather widely separated portions of the skeleton. It will be noted that the clavicle was involved on the opposite side from the cervical lymph node involvement. The patient is still under treatment and no evident lymph node involvement has occurred on the left side of the neck.

DISCUSSION

Figure 3 yields data which we have interpreted as indicating widespread irritation of the bone marrow due to focal lesions of Hodgkin's lymphogranuloma. Whether these focal granulomatous lesions are due to metastases from lesions outside the marrow or arise in situ from the agent responsible for the lesions of Hodgkin's disease is not clear at the present time.

In 1924 Symmers[6] reported, "The bone marrow in Hodgkin's disease may react in at least two different ways: (*a*) it may show hyperplastic changes, particularly in the eosinophiles, and eosinophilic myelocytes; or (*b*) it may be replaced by tissue of identical composition with that of the diseased

lymph nodes, sometimes over an extraordinarily wide distribution." During,[7] in 1918, stated that while eosinophiles are not peculiar to Hodgkin's disease, there is no other condition in which they are found in such large numbers. Montgomery[5] (1928) concludes from his study "that marked eosinophilia in the tissue sections in Hodgkin's disease points to an essential irritation and involvement of the bone marrow in this disease and should lead to a careful examination of the osseous system in such cases."

These quotations are from authors reporting studies in Hodgkin's disease before marrow aspiration was in use as a practical method of marrow study. Their conclusions assume added significance when confirmed by the simple methods of marrow study available today and reported in detail in our present study.

Summary of Results

1. A cellular pattern, uniform in type, was demonstrated in the aspirated marrows of 59 patients with Hodgkin's disease. This pattern showed an increase of the myelocytic elements (a shift to the left) with emphasis on the neutrophilic and eosinophilic myelocytes, the band neutrophiles, eosinophilic segmented cells and the plasmacytes.

2. This same cellular pattern was present in the aspirated sternal marrow of 12 patients, 10 of whom showed Hodgkin's lymphogranuloma in the marrow at autopsy.

3. The marrows of 67 patients, including 18 autopsy cases, showed an increase of megakaryocytes, when enumerated by a special technic with an established normal. This increase of megakaryocytes we interpret as indicative of marrow irritation and possible degenerative cellular changes.

4. We believe the incidence of skeletal lesions shown by roentgenologic examination is necessarily incomplete and too low, as marrows with Hodgkin's lymphogranuloma may contain lesions too small to involve the adjacent cortical portion of the bone.

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INTRAVENOUS NEOSTIGMINE IN DIAGNOSIS OF MYASTHENIA GRAVIS *

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The diagnosis of myasthenia gravis has been made with ever increasing frequency since 1935 when Walker [1] demonstrated the remarkable therapeutic effect of neostigmine and Viets and Schwab [2] described its diagnostic use.

Prior to 1942 there were only four cases on our records. In the past five years 23 more have been diagnosed. These cases will be reported later. The purpose of this paper is to present a modification of the neostigmine diagnostic test described by Schwab and Viets.[3] Their test consists of the intramuscular injection of 1.5 mg. of neostigmine methylsulfate combined with 0.6 mg. of atropine sulfate in a single "diagnostic" ampule. The injection is followed by an hour of observation at 10 minute intervals "scoring" the patient on both the subjective and objective improvement.

In our experience with this test, the initial response began in 15 to 30 minutes and maximal improvement was unpredictable often coming an hour or more after injection. It seemed possible that intravenous neostigmine might give a more prompt and complete response.

A thorough study of neostigmine toxicity was reported by Aeschlimann and Reinert [4] in 1931. They found that the dose of neostigmine causing 50 per cent mortality in mice was 12 to 16 mg. per kg. orally, 1 mg. per kg. subcutaneously and 0.45 mg. per kg. intravenously.

No fatalities attributable to neostigmine were found in the literature up to 1942.† A personal experience by Goodman [5] was reported in 1937. He took 45 mg. of neostigmine bromide by mouth and had an unpleasant, apparently parasympathetic, reaction terminated by atropine.

No reported clinical experience with intravenous neostigmine could be found up to 1942. Since that time, however, Bennett and Cash [6] have advised rapid intravenous neostigmine to offset the curare effect in their diagnostic test (1943). Viets,[9] in 1944, reported the administration of neostigmine by slow intravenous drip to a seriously ill myasthenic.

It seemed to us that the promise of a better diagnostic test offset what appeared to be a minimal risk. As neostigmine is apparently twice as toxic

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From the Department of Medicine, Indiana University Medical Center.
The author expresses his appreciation to the Hoffmann-La Roche Company for generously furnishing most of the neostigmine ("Prostigmin") used in this series.

† Addendum: Since the writing of this paper, a fatality, presumably due to the intramuscular injection of 1 c.c. (0.5 mg.) of neostigmine, has been reported.[12] That this was probably an example of unusual individual susceptibility was mentioned by Dr. Merrill and further stressed by me in a letter to the Editor of the Journal of the American Medical Association.[13] In this letter immediate use of atropine, intramuscularly or intravenously, for any untoward reaction to neostigmine was reëmphasized.

intravenously it was decided that only one third the intramuscular dose should be used. Accordingly, on June 8, 1942, 0.5 mg. (1 c.c. of 1/2000 solution) of neostigmine methylsulfate was given intravenously to an 18 year old girl complaining of ptosis, diplopia, dysarthria, dysphagia and general incapacitating muscular weakness of four years' duration. Within 15 seconds she said distinctly, "I don't see double anymore." Within two minutes her ptosis and myasthenic facies had disappeared completely and she demonstrated normal muscle power and swallowing ability. There were no untoward reactions to the drug.

The Intravenous Test

A thorough history is taken with special emphasis on ptosis, diplopia, dysarthria, dysphagia and general muscular weakness variable with rest and fatigue, menstruation, pregnancy, acute infections and emotional upsets.

On examination one should study the degree of ptosis, limitation of extra-ocular movements, ability to smile, whistle, distend the cheeks, chew gum, swallow liquids, count to 100, maintain grips, lift, walk and step up on a chair or stool. Each of these performance tests should be repeated sufficiently to detect abnormal fatigability. The results should be carefully recorded.

If the history and physical findings are sufficiently characteristic of myasthenia gravis, 1 c.c. of a 1/2000 solution (0.5 mg.) is injected intravenously within a timed 1 minute period. Improvement in a true case of myasthenia gravis often begins before the needle can be withdrawn and is usually maximal in at most five minutes (figures 1 and 2). Therefore, the performance tests should be repeated after five minutes have elapsed and the degree of objective improvement recorded. Subjective improvement is not considered, thus lessening the possibility that a psychic response to an injection might result in a false positive diagnosis. Occasionally, in very mild true myasthenia gravis the response to an intravenous dose of 0.5 mg. of neostigmine is doubtful or minimal. In such an instance the test should be repeated on the following day with 1 mg. provided there were no untoward reactions to the 0.5 mg. dosage.

Atropine sulfate, usually 0.6 mg., should always be kept at hand and should be injected subcutaneously whenever side-effects become manifest, but is never to be injected with the neostigmine. Viets [10] has stated that marked side-effects from neostigmine almost disprove a diagnosis of myasthenia gravis, and our experience has been similar. However, these side-effects, although uncomfortable, are apparently not dangerous and we do not, as Viets advises, use atropine simultaneously with neostigmine to offset them. We feel that these reactions, however uncomfortable, are highly valuable diagnostically.

In the past five years we have given neostigmine intravenously on several hundred occasions, not only as a diagnostic test for myasthenia gravis but also to arthritics and neuro-muscular cases. The only side-effects worthy

of note were encountered in non-myasthenic individuals and in those with extremely mild myasthenia gravis. These consisted of mild abdominal cramping, muscle fibrillations, flushing and sweating, dizziness, mild nausea and diarrhea. The heart rate was slowed but never more than 10 beats per minute and the drop in blood pressure was negligible. These reactions were stopped, without exception, within 10 to 15 minutes by the subcutaneous injection of 0.6 mg. of atropine sulfate.

We have seen several cases with extremely mild involvement or in partial or complete remission, in which the past history justified further study. In some of these even 1 mg. of neostigmine intravenously gave an indefinite response. In such cases the Curare test,[6, 7, 8] the Jolly test, muscle biopsy and barium swallow under fluoroscopy [10] have proved highly valuable. Also of some merit is a therapeutic test of a week of oral neostigmine bromide.

A preliminary report of the diagnostic use of neostigmine in myasthenia gravis was presented by the author in a case discussion published in January, 1947.[11]

The intravenous administration of neostigmine has consistently given more rapid, clear cut, complete improvement in cases of myasthenia gravis than we have been able to obtain with the intramuscular route as advised by Viets. A direct comparison of these methods is illustrated in figure 1. Patient 18, a 53 year old truck driver, experienced a sudden onset of severe myasthenia gravis in January, 1946, with marked diplopia and ptosis. The disease had rapidly progressed to total involvement with severe dysphagia, dysarthria and general muscular weakness when he was first seen on May 22, 1946. At the height of the disease the patient required 60 tablets of neostigmine bromide (900 mg.) daily for maximal improvement without intolerance. At the time figure 1 was taken this patient was in partial remission which has since become complete. On February 6, 1947, he was photographed after 18 hours without medication. Then 1.5 mg. of neostigmine methylsulfate and 0.6 mg. of atropine sulfate were injected intramuscularly. The patient was photographed two minutes later and then at five minute intervals for one hour. The same procedure was followed on February 7, 1947, except that 0.5 mg. of neostigmine methylsulfate was injected intravenously and no atropine was used. Two minutes after 0.5 mg. of intravenous neostigmine he showed maximal improvement whereas 60 minutes after an intramuscular dose three times as large he showed only a partial response.

Another example of the rapid effect of intravenous neostigmine is shown in figure 2. Patient 24, a 5 year old boy, experienced a sudden onset of ptosis, dysarthria, dysphagia and general muscular weakness on November 7, 1946. The referring diagnosis was tuberculous meningitis. On November 20, 1946, 0.25 mg. of neostigmine methylsulfate was injected intravenously and the patient showed complete recovery of all muscle function within three minutes. Figure 2 is taken from a 16 mm. colored motion picture film.

"A" shows the patient's condition without medication for 18 hours. "B" shows complete recovery 42 seconds after the intravenous injection of 0.5 mg. of neostigmine. This dose was well tolerated by the patient and it will be noted that his reaction was much faster than when 0.25 mg. was given.

FIG. 1. (1–6) Patient 18 in relapse, and two, five, 15, 30 and 60 minutes after 1.5 mg. of neostigmine and 0.6 mg. of atropine sulfate intramuscularly. (7–9) Patient 18 in relapse, two and 15 minutes after 0.5 mg. of neostigmine intravenously.

This rapid complete response is demonstrable not only in the facies and the extraocular muscles but also in masticatory, pharyngeal, laryngeal and skeletal musculature.

In our experience, intravenous neostigmine has given better results in the performance of the fluoroscopic barium-swallow test for dysphagia [10]

A B

FIG. 2. (*Left*) Patient 24 in relapse. (*Right*) Patient 24, 42 seconds after 0.5 mg. of neostigmine intravenously.

than has intramuscular neostigmine. When barium is retained in the upper esophagus, 0.5 mg. of neostigmine is injected intravenously. If the dysphagia is due to myasthenia gravis, a return to normal swallowing can be visualized in a few minutes instead of the 20 minutes or more required with intramuscular administration.

By use of the intravenous method we have been able to illustrate dramatically the effect of neostigmine upon the myasthenic individual in a series of motion pictures taken for teaching purposes.

Medication is with-held from the patient for a period of 18 to 24 hours preceding the test. Before the injection, the routine performance tests and a "close-up" of the patient's face are filmed. Then, with the camera in continuous action, 0.5 mg. of neostigmine is administered intravenously. The performance tests are repeated at the height of the improvement which usually occurs within a few minutes. Due to the rapid and complete response to intravenous neostigmine, the progress of the patient can be recorded without the time lapse required when the intramuscular method is used.

Intravenous neostigmine has been used in the diagnosis of 24 of the cases of myasthenia gravis in our series in the past five years. Of these, 21 or 87.5 per cent, reacted sufficiently for a positive diagnosis. Only three patients failed to react. One gave a history of previous typical severe myas-

thenia gravis with respiratory failure requiring a respirator. She was seen in complete remission and failed to react to intravenous neostigmine. The Jolly and Curare tests were also negative but the muscle biopsy was considered typical of myasthenia gravis. The second non-reactor had extremely mild symptoms. The Jolly and Curare tests were positive, however, and he has since responded well to oral neostigmine. The third non-reactor gave a typical history of previous severe myasthenia gravis but was seen in complete remission during his hospitalization for duodenal ulcer. His diagnosis was made on the basis of a typical history and positive Jolly and Curare tests. Objective improvement in all of the 21 reactors following 0.5 mg. of neostigmine intravenously was so rapid and clear-cut that no other diagnostic methods were necessary except to otherwise confirm a positive diagnosis.

Our experience with intravenous neostigmine in the diagnosis of myasthenia gravis leads us to believe that it has the following advantages over the intramuscular diagnostic test:

1. It gives a more rapid complete response which lessens the possibility of a false negative diagnosis in a mild case.
2. Only objective responses need be considered which diminishes the risk of false positive diagnoses.
3. The quick, clear-cut response should facilitate office diagnosis by a busy practitioner and aid in demonstration of cases for teaching purposes.

Summary and Conclusions

1. A new diagnostic method for myasthenia gravis using 0.5 mg. of neostigmine intravenously instead of 1.5 mg. intramuscularly, as advised by Schwab and Viets, is presented.

2. Neostigmine has been injected intravenously in several hundred cases, both myasthenic and non-myasthenic, without any serious reactions in the dosage range used.

3. Intravenous neostigmine has given objective diagnostically positive reactions in 21 out of 24 cases of myasthenia gravis in our series, or 87.5 per cent.

4. We have obtained better results with intravenous than with intramuscular neostigmine in the performance of the barium-swallow test for dysphagia due to myasthenia gravis.

5. Our experience indicates that intravenous neostigmine is superior to intramuscular neostigmine in the diagnosis of myasthenia gravis, as it gives more rapid, clear-cut and complete improvement in even the mildest cases and enables the observer to use objective criteria alone.

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CASE REPORTS

PRIMARY SARCOMA OF THE HEART WITH REPORT OF A CASE *

By PALMER A. SHELBURNE, M.D., *Greensboro, North Carolina*

EIGHTY-TWO cases of primary sarcoma of the heart have been found to be reported prior to December, 1946, including 76 cases collected in excellent reviews of the literature by Perlstein,[1] Yater,[2] and Weir.[3] Antemortem diagnosis has been made in only five cases.[5] It is the purpose of this report to relate the clinical course and to describe bizarre manifestations in a patient who died of this disease after six months' observation.

CASE REPORT

W. H. V., a white man, American, aged 29, married, was admitted to the Wesley Long Hospital, Greensboro, North Carolina, June 23, 1946, complaining of left anterior chest pain. The present illness was of 10 days' duration with sore throat,

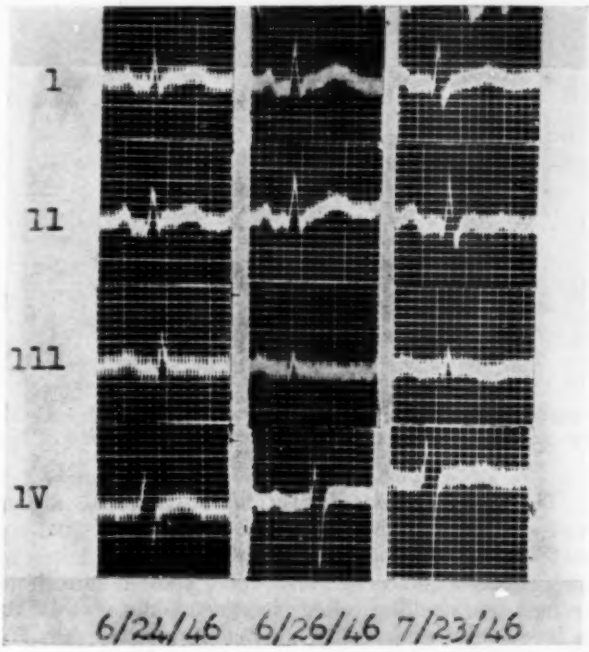

FIG. 1. Electrocardiographic tracings. June 24, 1946. Rate 120, voltage low in limb leads. PR interval .16 second. June 26, 1946. Low voltage is suggestive of pericarditis but may occur in normal hearts, myxedema and severe myocarditis. July 23, 1946. Rate 80. Digitalis effect. PR interval .18 second. T-wave inverted in Lead III and flat in Lead II.

* Received for publication June 13, 1947.

cough and low fever, but he had been able to work until three days prior to admission. He had had fever and chills at the age of 15 years, diagnosed as tertian malaria; an abscessed tooth with drainage for one year; and during the same period of time suffered three attacks of momentary unconsciousness, preceded by weakness and irregular pulse, with apparent improvement following ingestion of food rich in carbohydrate.

Physical Examination. Cyanosis and dyspnea were evident. Temperature was 100.5° F. Blood pressure was 90 mm. Hg systolic and 75 mm. diastolic. The area of cardiac dullness was enlarged. The left border was in the sixth intercostal space, 4 cm. to the left of the midclavicular line, the right border 4 cm. to the right of the

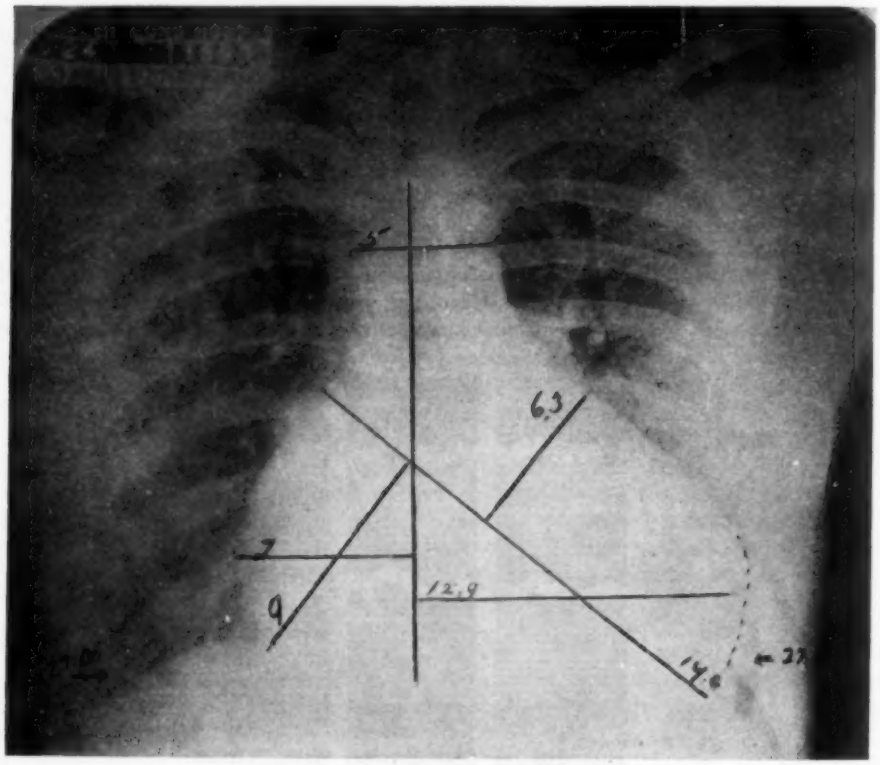

FIG. 2. Roentgenogram. Cardiac silhouette is enlarged. Note absence of mitral configuration and the more or less symmetrical "leather-bottle" outline of heart shadow.

midsternal line. The apex beat was diffuse, the heart sounds distant, and a friction rub could be heard and felt over the base of the heart. Bronchial breathing and dullness could be heard just below and medial to the tip of the left scapula (Ewart's or Bamberger's sign). The left knee was tender and showed some limitation of motion. There was no redness nor swelling. Red blood cell count was 4,790,000; hemoglobin 15 grams; white blood cell count 15,200; polymorphonuclear cells 76; eosinophiles 1; small lymphocytes 23 per cent. Sedimentation rate was 22 mm. in one hour (Cutler); Kahn reaction was negative; blood culture was sterile after five days.

Clinical Course. A pericardial paracentesis was performed on the second and fourth hospital days because of great dyspnea. A total of 2100 c.c. serosanguineous fluid was obtained. In each instance withdrawal of fluid relieved dyspnea, slowed

the pulse rate to 100, and raised the blood pressure to 120 mm. Hg systolic and 80 mm. diastolic. The fluid clotted after standing 24 hours. A guinea-pig was injected in an effort to learn if the condition were tuberculous. From time to time there could be heard varying types of heart sounds over the chest; systolic and diastolic mitral murmurs and pericardial friction rubs, each of which showed great variation and even disappearance with time and change of position. A tentative diagnosis of rheumatic fever or generalized septicemia was made.

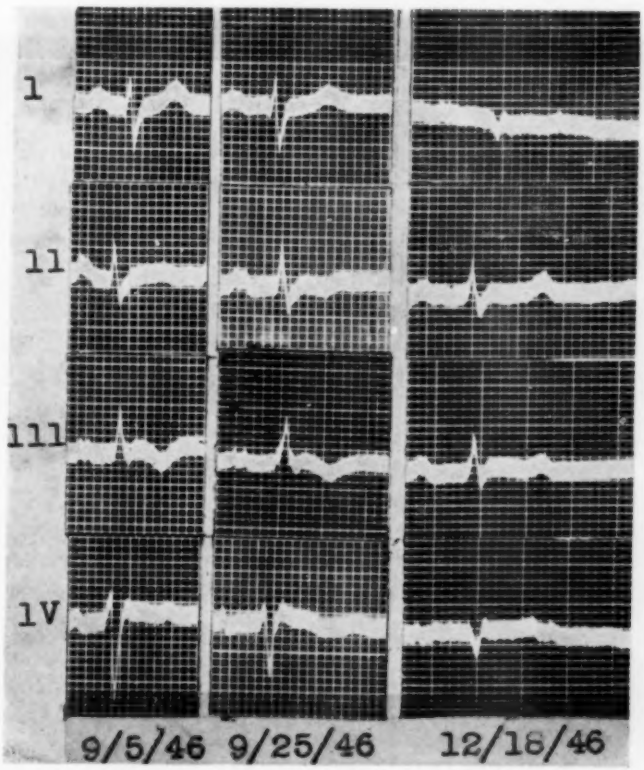

FIG. 3. Electrocardiographic tracings. September 5, 1946. A shift from normal axis to right axis deviation had become evident. PR interval 0.2 second. September 25, 1946. Rate 60. T-wave in Lead II and Lead III inverted. Notching of P-wave in Lead II. December 18, 1946. Rate 50. PR interval 0.24. Beginning auricular ventricular block. T-waves in Lead II and Lead III now upright. Inversion and return to normal are suggestive of myocardial infarction. The electrocardiographic tracings were not typical of any disease entity.

Medication consisted of sodium salicylate and sodium bicarbonate, of each 1.3 gm. (20 grains), every four hours. Pantopon 0.002 gm. (⅓ grain) was required for chest and joint pain. The joints involved were, alternately, the knees, the right shoulder, and the right elbow. There was no swelling or redness of the involved joints. Roentgenogram of the right shoulder was negative. Salt restriction, with limitation of fluid, prevented further pericardial effusion.

On the seventh day of illness the patient was sitting erect in bed when a dramatic episode occurred. Pulse deficit for the first time had been noted. A few minutes following this observation the patient suddenly became pale, then cyanotic, then lost

consciousness. The radial pulse was slow and irregular. The heart sounds were distant, irregular and of slow rate. Death seemed imminent. A convulsive seizure lasting 10 minutes followed, and the patient was forcibly held in bed. Death may have been averted by the following procedures: Patient was placed in the Trendelenburg position; adrenalin was given by intravenous injection, oxygen and artificial respiration. Finally the patient gave a forceful expiratory grunt; the heart rate increased until accurate counting was impossible and consciousness was regained. The paleness, slow irregular heart beat and syncope were suggestive of Adams-

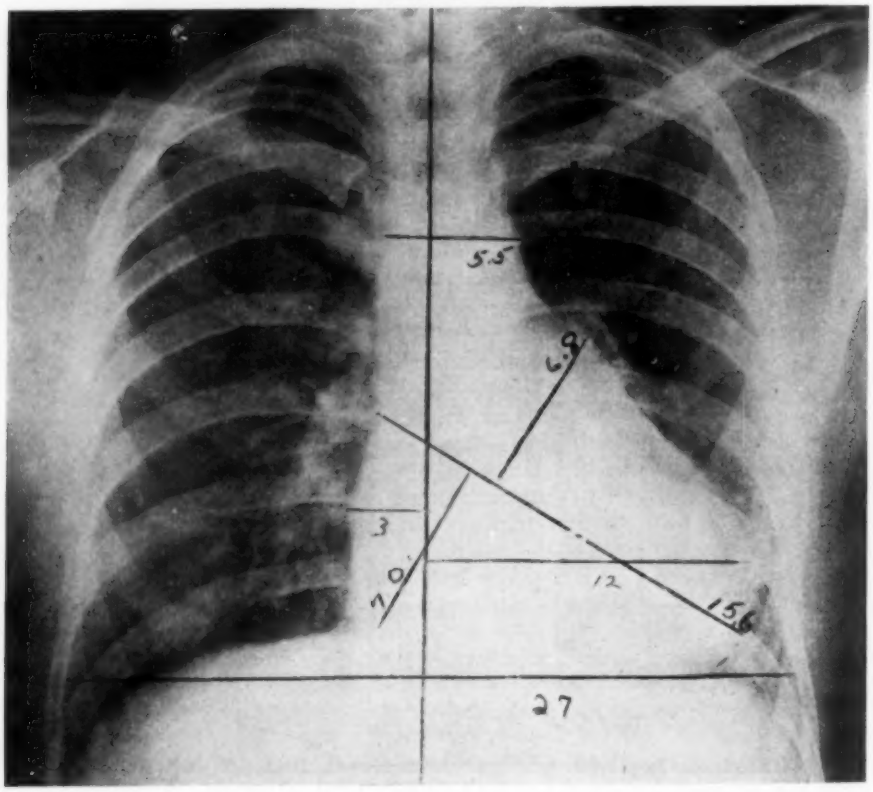

FIG. 4. Roentgenogram. There is no evidence of pericardial effusion at this time. The right border of the heart is normal, but the left border is definitely prominent and has a mitral configuration.

Stokes syndrome. The rapid heart rate was suggestive of ventricular tachycardia. A satisfactory explanation of the cardiac arrhythmia could not be made at the time of its occurrence. The patient stated that on three occasions in the past year he had experienced weakness, irregular pulse and momentary unconsciousness, and that ingestion of food rich in carbohydrates appeared to aid in recovery. Because of this history glucose was given intravenously. Repeated blood sugar determinations, however, suggested this attack was not due to hypoglycemia.

Following this attack the patient was digitalized and a daily maintenance dose of .2 mg. digitoxin was given. In spite of this the pulse remained 80–100. At intervals oxygen was administered to combat cyanosis and dyspnea. A total of 25,-

000,000 units of penicillin was given because of the possibility of septicemia, originating from the abscessed tooth, and bacterial endocarditis, although repeated blood cultures had been negative. Nitroglycerine at times gave prompt relief from cardiac pain.

After four months of illness there was no noticeable improvement, and it was suggested that the patient enter one of the large clinics for further study. Two months' stay at the clinic resulted in the diagnosis of rheumatic fever.

The sedimentation rate ranged from 22 mm. to 68 mm. in two hours (Cutler method), the white blood cell count from 12,000 to 21,000 per cu. mm. The urine showed increasing albumin after four months of illness. Proteins of the blood, red

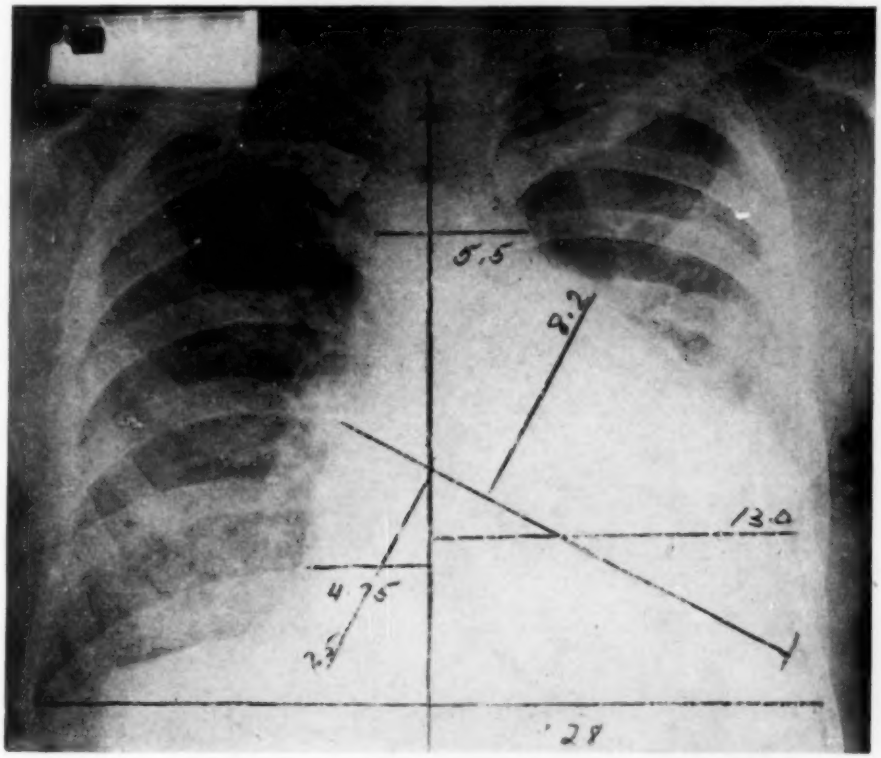

FIG. 5. Roentgenogram. This radiograph was taken two and one-half months after the previous one. Note the progressive enlargement and wavy character of the left border of the heart and loss of the mitral configuration.

blood cells and hemoglobin were kept at normal levels by blood transfusions. The abscessed tooth was removed on the fifty-fifth day of illness and culture of material obtained from the socket showed mixed organisms with hemolytic streptococci predominating. Cultures of blood and pericardial fluid were sterile. The guinea-pig was alive and well after two months and upon sacrificing the animal no evidence of tuberculosis was found.

A septic temperature ranging from normal to 103.5° F. was maintained throughout the illness, with the exception of a few days of normal temperature. For a short time the patient's mental status was unsatisfactory. This was found to be due to the cumulative effect of phenobarbital. Pulse range was from 40 to 60, average 80

FIG. 7. Section showing left side of heart with extensive involvement of auricular walls and focal areas of tumor in the ventricular wall.

FIG. 6. Heart sectioned to show necrotic tumor making up thickened right ventricular wall, and (A) tumor mass projecting into cavity.

to 100 under digitalization, 40 to 120 when this drug was not being administered. Digitalis was discontinued after three and one-half months of administration. Three weeks later an unexpected bradycardia of 40 to 50 was noted. This slow rate continued for two weeks and reappeared when evidence of heart block was noted.

After five months of illness, graduated exercises were prescribed but were soon discontinued when the cardinal symptoms of heart failure developed. An interesting feature was the almost entire limitation of edema to the face and upper extremities. The patient became unconscious December 17, 1946 and died in cardiac failure after 180 days of illness.

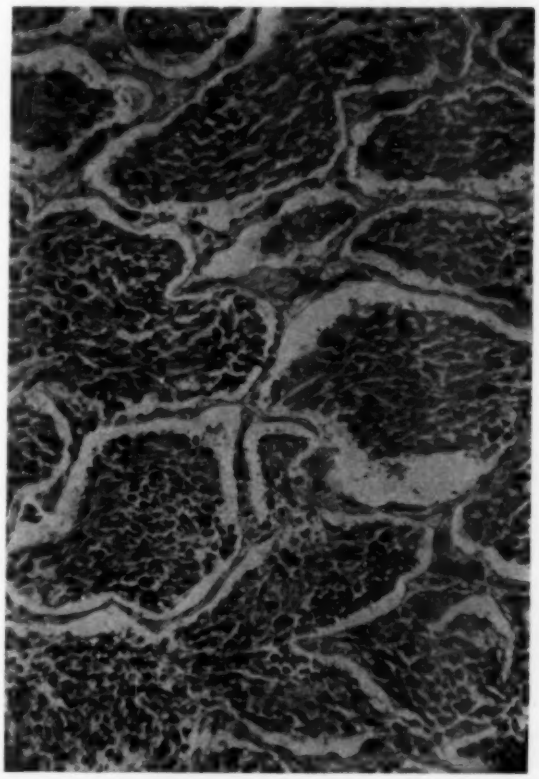

FIG. 8. Low power view of metastatic lesion in right lung.

Autopsy Report. The significant findings at autopsy were a moderate generalized anasarca, bilateral hydrothorax, and some ascitic fluid in the abdominal cavity.

Lungs: Both lungs showed some atelectasis as well as considerable congestion. In the peripheral portion of the right lung were four small well-demarcated tumor nodules varying from 5 mm. to 10 mm. in diameter.

Heart: The pericardial cavity was completely obliterated by old fibrous adhesions. The heart with its pericardial covering weighed 1500 grams, its shape was greatly distorted, its surface nodular. Upon opening the heart the right auricular cavity was found to be greatly enlarged, and the wall thickened by an infiltrating tumor. The right ventricular wall was practically replaced by a neoplastic growth which showed extensive necrosis. Practically the entire myocardium had been replaced by tumor

tissue and the wall measured up to 10 cm. in thickness. There was a large tumor mass, rather necrotic, growing from the wall into the right ventricle, practically filling this chamber, and pointing upward, partially occluding the orifice of the pulmonary artery. The left side of the heart showed extensive involvement of the auricular wall, this averaging 3.5 cm. in thickness. There were also isolated areas of tumor tissue in the myocardium of the left ventricle. The valves all appeared competent and showed no evidence of disease. The liver and spleen showed congestion.

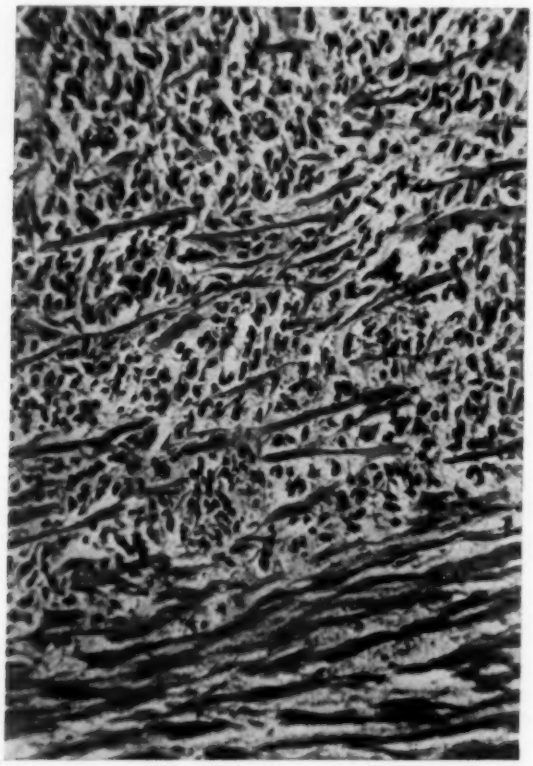

FIG. 9. Low power view of primary tumor in the myocardium.

Microscopic study of the heart sections and the tumor masses found in the lungs revealed that they were neoplastic growths made up of ovoid and spindle-shaped cells. Extensive necrosis affected a greater part of the tumor tissue. The myocardium showed definite invasion by the neoplastic process. No demonstrable striations of the tumor cells were found.

Pathological Diagnosis: Primary fibrosarcoma of the heart, with pulmonary metastases.

COMMENT

Tumor tissue with its attendant edema involving the entire wall of the right auricle may have interfered with impulses reaching the sino-auricular node producing bradycardia. A similar interference with the conduction system distal to the sino-auricular node may have caused beginning auriculoventricular block.

The growth of tumor tissue into the cavity of the right ventricle was of sufficient size to close the pulmonic valves momentarily. It is possible that the attack of unconsciousness was produced by stoppage in the flow of blood through the heart in this manner and that relief followed a change in position.

Differential Diagnosis. Negative blood and pericardial fluid cultures, a normal guinea-pig two months after injection with pericardial fluid, negative lung fields and negative tuberculin test elminate septicemia, tuberculous pericarditis and subacute bacterial endocarditis. Lack of evidence of enlargement of the spleen or of the mediastinal glands, and the moderate increase in number of white

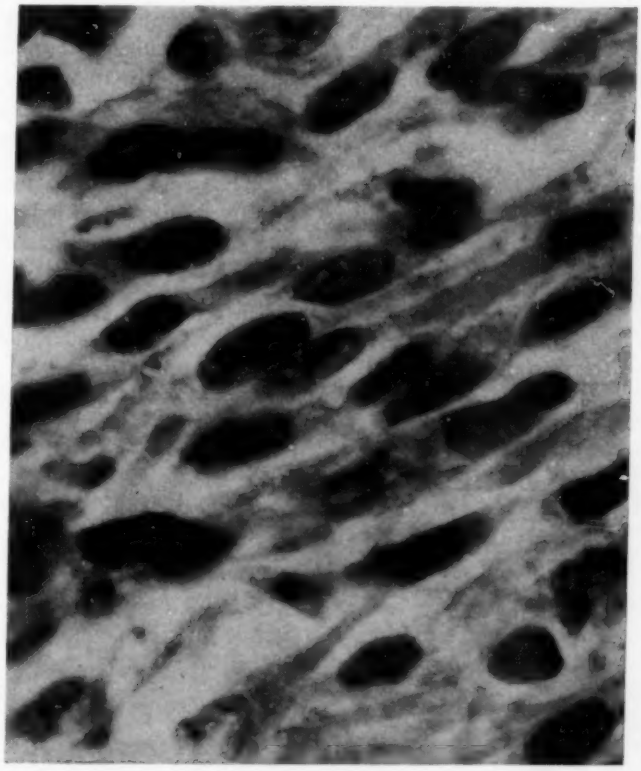

FIG. 10. **High power view of myocardial tumor** showing a typical area of sarcomatous process.

blood cells with a normal differential count, were considered sufficient to eliminate leukemia and Hodgkin's disease as a cause of the pericardial effusion early in the illness. Rheumatic fever was considered the most likely diagnosis because of the following findings: *Major manifestations* (1) carditis, evidenced by pericardial effusion, enlargement of the heart, and decompensation; prolongation of auriculoventricular conduction time, T-wave inversion, low voltage, sinus tachycardia and bradycardia; and (2) arthralgia preceded by sore throat. *Minor manifestations* (1) fever, (2) precordial pain, (3) increased white blood cell

count, and (4) increased sedimentation rate. It was recognized that rheumatic fever did not explain the complete picture. Recurring attacks of syncope and unconsciousness, and bradycardia were manifestations requiring autopsy for adequate explanation.

The sudden onset of signs of intractable heart disease in a young person without a history of preëxisting cardiac disease, with no discoverable basis for the disease; a rapidly forming serosanguineous pericardial fluid; postural alteration in murmurs and pericardial friction rubs; roentgenologic evidence of increasing heart enlargement and irregularity of shape; failure of pulse rate to respond to adequate digitalization; attacks of syncope; cardiac arrhythmias, including sinus tachycardia, bradycardia and beginning heart block should lead one to consider neoplasm of the heart as a possible cause of the disease under consideration. The finding of cancer cells in the pericardial fluid enables one to make a positive diagnosis, but, unfortunately, this study was not made in this case.

Summary

A case of primary fibrosarcoma of the heart is reported. Attention is called to bizarre clinical manifestations which, possibly, might have led to antemortem diagnosis.

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A CASE REPORT OF METASTATIC CARCINOMA TREATED WITH TEROPTERIN *

By Max J. Klainer, M.D., F.A.C.P., *Stoneham, Massachusetts*

In the years prior to the use of sulfonamides and more especially to the use of penicillin, infrequent reports of "cures" of individual cases of subacute bacterial endocarditis appeared in medical literature. As with subacute bacterial endocarditis in former years, metastatic carcinoma invariably has been fatal so that any therapy which gives a modicum of evidence of checking the spread of this fatal disease deserves consideration. It is, therefore, of interest to report a case of metastatic adenocarcinoma which apparently had been temporarily arrested and by the use of a new chemotherapeutic approach.

Case Report

A 39 year old Armenian housewife first was seen in February 1947 because of severe, agonizing pains originating in the region of the lower lumbar spine and

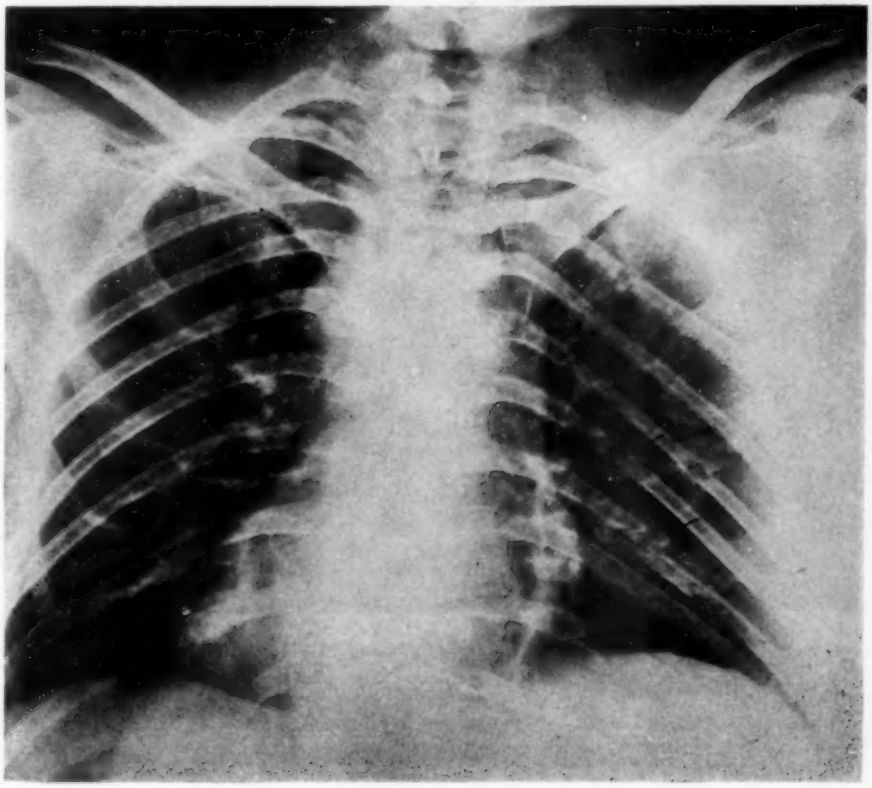

Fig. 1.

* Received for publication December 26, 1947.

Teropterin is the name given by Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York for pteroyl triglutamic acid.

FIG. 2.

radiating down the posterior aspect of the left thigh and left leg to the heel. A left radical mastectomy had been performed by Dr. Richard Miller at the Massachusetts General Hospital, Boston, in December 1944 because of an adenocarcinoma Grade III with spread to the axillary lymph nodes. The patient had made a good recovery from the operation and had done well until March 1946 when pain developed in the region of the mid-lumbar spine, and roentgen-ray studies revealed a destructive process in the third lumbar vertebra. The patient then was given radiotherapy over a period of several months without any appreciable improvement. Roentgenographic

studies repeated in September 1946 showed extension of the process in the third lumbar vertebra and new areas of destruction in the dorsal vertebrae and the ribs. A diagnosis of metastatic carcinoma was made and the patient placed on narcotic medication for relief of pain. However, she became progressively worse and soon was bedridden. She was unable to make the slightest movement without severe pain.

The patient's condition seemed hopeless and she was hospitalized primarily for the purpose of being kept as comfortable as possible. On admission to the Sanitarium and Hospital, Stoneham, Massachusetts, the patient proved to be a trying nursing problem. Only by lying quietly on her right side with her knees drawn to her abdomen could she endure her pain. Changing the bed linen, bathing, and the use of the bedpan were almost impossible. In addition she sweated profusely, necessitating frequent changes of the sheets. One hundred mg. demerol and dilaudid in doses of grains 1/16 every four hours only partially controlled her pain.

FIG. 3.

Physical examination at the time of admission revealed percussion tenderness along the lower dorsal and lumbar vertebrae and along the course of the left sciatic nerve. The eyes, ears, nose and throat, heart, lungs and upper extremities were all within normal limits. The blood pressure was 140 mm. of mercury systolic and 90 diastolic. The temperature 98.6°, pulse 100 and respirations 20 per minute.

Initial laboratory studies disclosed the following: hemoglobin, 12 gm. (77 per cent Sahli); red blood count, 3,660,000; white blood count, 5,450 with 40 per cent polymorphonuclears and 58 per cent lymphocytes. The total serum protein was 6.3 grams with 3.0 grams albumin and 3.3 grams globulin. No Bence Jones protein was found

in the urine, and the urinalyses were not otherwise remarkable. In spite of extensive bone destruction the acid phosphatase was essentially normal, 4.5 King units.

Roentgen-ray films of the dorsal and lumbar spine, ribs and pelvis showed innumerable areas of bone destruction with pathological fractures of several of the ribs and of the eighth dorsal and second and third lumbar vertebrae (figures 1, 2 and 3). Areas of bone destruction also were found in the skull and in the right scapula. In an effort to check further bone destruction, the patient was placed on 50 mg. testosterone propionate and 20 mg. Teropterin three times a day, each being administered intramuscularly.

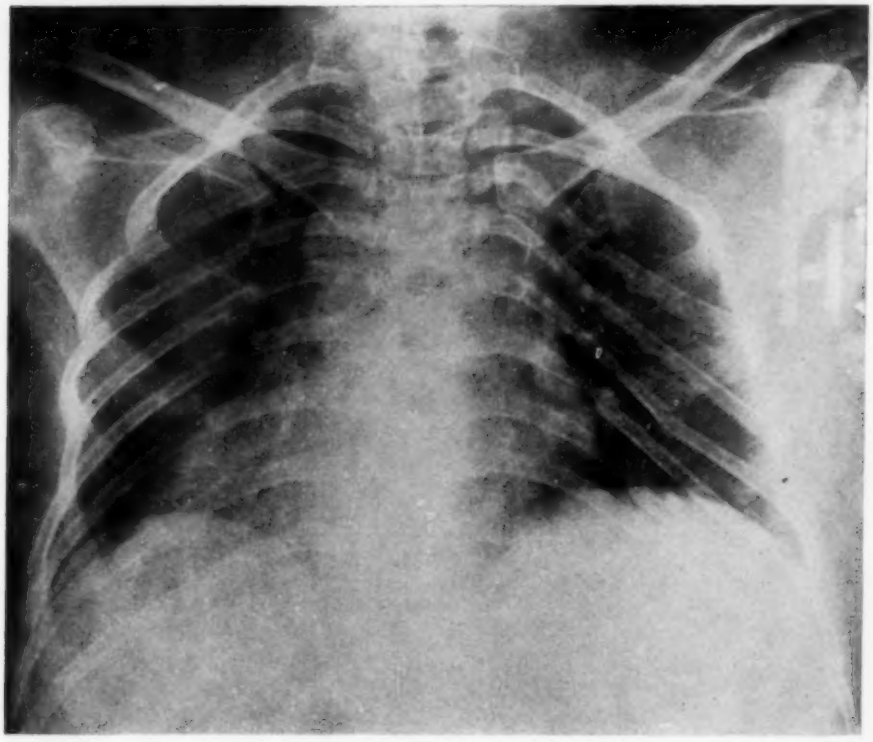

FIG. 4.

During the first week of her hospital stay the patient had her usual menstrual period and with the onset of the menses the pain increased markedly. An oophorectomy appeared advisable, and this was performed successfully on March 3, 1947 by Dr. Raymond Auvil of the hospital staff. At the time of operation the uterus was found to be enlarged, but there were no masses in the liver or elsewhere in the abdomen. Pathological studies of the removed tissues revealed normal Fallopian tubes but sections of the ovaries showed foci of metastatic adenocarcinoma.

In the first two weeks following operation the patient showed little change and she continued to require large doses of narcotics for relief of pain. During this time, however, the testosterone propionate was reduced to 100 mg. daily but the Teropterin was continued at 60 mg. daily. On March 17, 1947 she was given a transfusion of 500 c.c. of citrated blood with prompt return of the hemoglobin and red count to normal levels.

The first evidence of improvement was noted on March 19, 1947. The pain became less marked, the sweats were markedly reduced, and the patient became more cheerful. About March 23 she suffered a slight setback with accentuation of pain, but this was attributed to her expected menstrual period. Immediately thereafter

FIG. 5.

progressive and marked improvement was noted. By April 1, 1947 practically all narcotic medication for relief of pain was eliminated and the testosterone medication completely discontinued. The patient now received only Teropterin intramuscularly, while barbiturates were given for sedation and aspirin compound tablets for control of pain. During the period of testosterone therapy this patient did develop secondary sex changes such as hirsutism and deepening of the voice. These, however, slowly disappeared upon discontinuance of this drug. On April 11 this patient, who

had been unable to move without extreme pain, changed position freely in bed. On April 14 she sat up in a wheel chair.

Repeat roentgen-ray studies of the involved bones done on April 20 were interpreted as follows: "Reëxamination of the skeletal system shows no significant increase in the areas of bone destruction. As a matter of fact several of the previously described areas of bone destruction appear smaller and there is new bone formation seen in several areas where the destruction was markedly pronounced. Several of the pathological fractures show evidence of bony regeneration. The compression fractures of the second and third lumbar vertebrae are still present as previously described but the bone structure is somewhat denser" (figures 4 and 5).

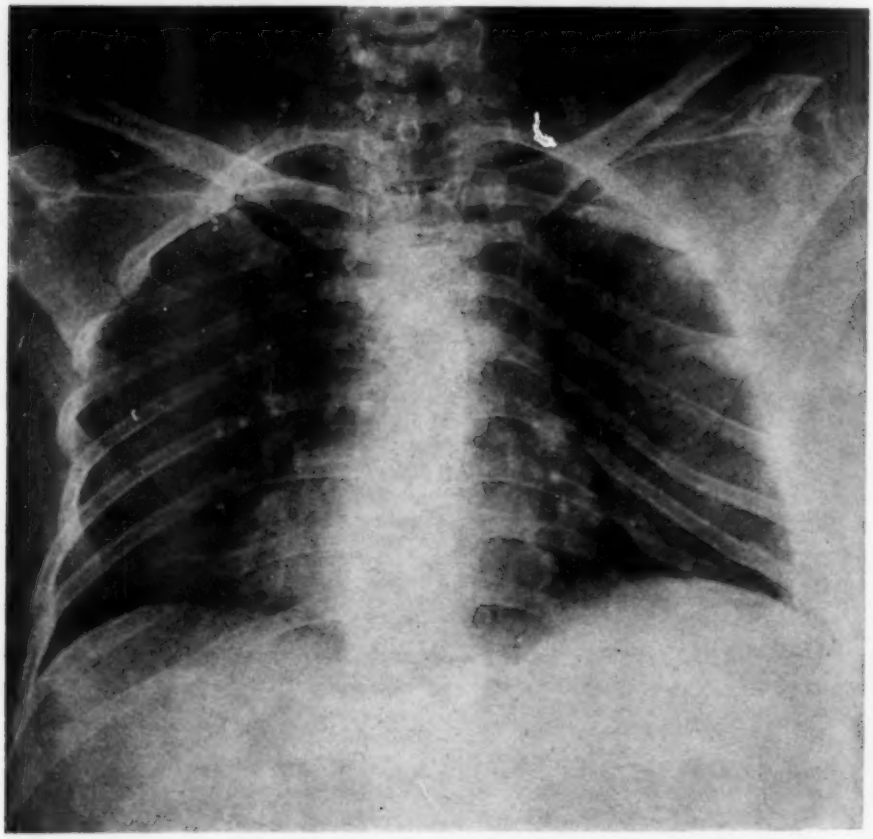

FIG. 6.

In May 1947 the patient was measured for a back brace. On May 14 she was allowed to walk first with the aid of a walker, and then with a cane only. This increase in activity produced no increase in the small amount of residual discomfort, and on June 5, 1947 she was discharged home on a maintenance dose of Teropterin 20 mg. b.i.d.

Roentgen-rays taken at the time of discharge were interpreted as follows: "Films of various bones show a remarkable change in the appearance of the bone structure with disappearance of many of the previously described areas of bone destruction,

with recalcification of the bone and healing of many of the fractures, particularly of the ribs. The bone structure of the involved lumbar vertebrae has improved due to increased recalcification. The findings as a whole indicate a very marked improvement in the previously described findings of pathological fractures and metastases."

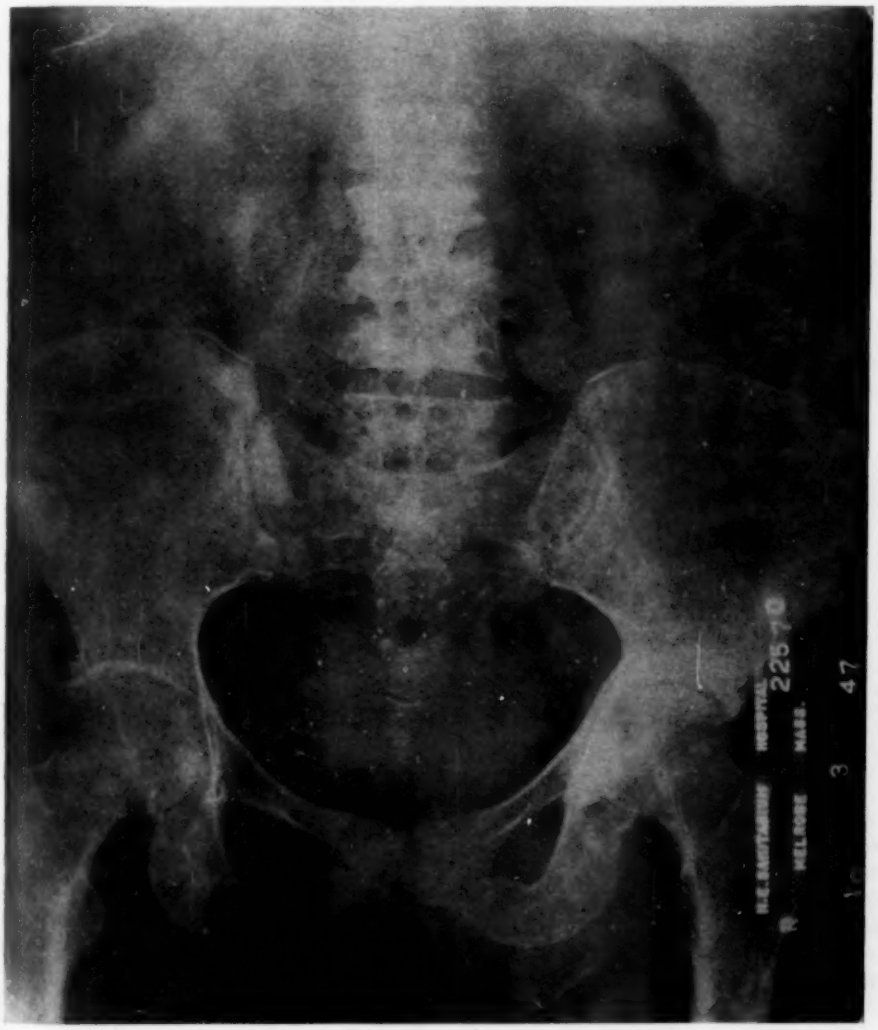

FIG. 7.

Following discharge from the hospital the patient continued to improve both clinically and by roentgen examination. Except for her back brace she was able to walk without the aid of any support and could perform many of her previous household duties. Except for transitory aching in the region of the left hip, which was readily relieved by an aspirin compound tablet, she was free of symptoms. The Teropterin medication was continued with a daily maintenance injection and she learned to

administer it to herself. Roentgen-ray films that were taken in October 1947 showed no new areas of bone destruction and further regeneration of bone formation in areas previously involved (figures 6, 7, and 8). In December 1947, the patient continued to show improvement, being completely ambulatory and complaining only of mild aching in the lumbar spine on prolonged standing or walking.

FIG. 8.

In January 1948, however, the patient returned to the hospital because of a recurrence of pain in several ribs on the left side and roentgenograms revealed new areas of metastasis involving multiple ribs. The Teropterin therapy was intensified for several weeks with some alleviation of the pain, but by March 1948 evidences of bone metastases were again present in the pelvis, vertebral column and left femur. The Teropterin no longer was able to control the pain and narcotic medication had to be resumed. The patient became increasingly depressed and voiced suicidal intentions. In May 1948 she threw herself forcibly from bed sustaining several pathological fractures and she died in shock within 24 hours.

An autopsy was performed and revealed gross involvement of the right breast, the lungs and the adrenal glands as well as of multiple bones. Microscopic study revealed that the carcinoma was scirrhous in character; that in the lungs the metastases showed areas of focal necrosis; in the bones along with extensive replacement and destruction there was evidence of new bone formation; and in all areas only occasional mitotic figures were seen.

SUMMARY

A case is reported of a 39 year old woman with metastatic spread of an adenocarcinoma, presumably originating in the breast, in whom the combined use of oophorectomy, testosterone propionate injections (given only during the first month of therapy), and injections of a new compound known as Teropterin (pteroyl triglutamic acid) produced definite clinical and roentgenological improvement which persisted for 10 months. The subsequent course of the patient was downward, and she died 14 months after therapy was instituted. Necropsy studies revealed gross involvement of the right breast, of the lungs, the adrenal glands and of multiple bones but microscopic studies revealed only occasional mitotic figures in the involved areas, evidences of focal necrosis in the metastatic areas in the lungs and evidences of new bone formation in the involved bones.

The author wishes to thank the medical and nursing staff of the New England Sanitarium and Hospital whose help in the management of this case was of great value.

Teropterin was supplied for clinical study by Dr. Y. SubbaRow, Director of Research, and his staff at Lederle Laboratories Division, American Cyanamid Company, to Dr. S. Farber of the Children's Hospital, Boston. I wish to express my thanks to Dr. J. Hawkins, formerly associated with Dr. Farber, for my original supply of this material.

THE DIAGNOSIS OF METASTATIC TUMOR BY CYTOLOGICAL EXAMINATION OF THE PERICARDIAL FLUID; REPORT OF A CASE USING SHORR'S STAIN*

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Albany, New York

METASTATIC tumors of the heart and pericardium are not uncommon. Reports of their incidence vary from 6.2 per cent to 10.9 per cent of all malignant disease.[1, 2] There are, however, few reports of the antemortem diagnosis of this condition, since such a diagnosis depends not only upon the suspicions of the clinician, but also upon the demonstration of neoplastic cells in the heart or pericardium. Perhaps the most important diagnostic aid is the cytological study of pericardial fluid. Pericardial effusion is often, though not regularly, present. Even by this method the number of instances in which an accurate antemortem diagnosis has been made is small, there being only 10 cases reported in the American literature.[3, 4, 5]

For some years we have been interested in the study of exfoliated cells in body secretions and fluids with particular reference to the demonstration of malignant neoplastic cells in such materials. The method employed is simple and has given us accurate results in a high percentage of cases, especially in the study of sputum.[6] The following case of bronchogenic carcinoma in which tumor cells were found in both sputum and pericardial fluid by means of stained wet films seems worth reporting.

* Received for publication April 6, 1948.

From the Departments of Anatomy and Medicine, Albany Medical College, Union University, and the Medical Service, Albany Hospital.

The method is Shorr's technic for the wet film study of vaginal smears.[7] Fresh material is spread on a glass slide and fixed before drying for a minimum of 10 minutes in a fixative made of equal parts of 95 per cent alcohol and ether. Smears of sputum must be made fairly thin if the mucus is tenacious and thick, as fixation as well as staining is difficult in these cases. Aspirated fluids are centrifuged and the sediment used; when smearing the sediments an attempt should be made to remove the buffy coat with a minimum of red blood cells as an excess of the latter element may completely obscure the other material. A second set of smears from fluid sediments is routinely fixed in a fixative made of 95 c.c. of the above alcohol-ether fixative to which has been added 10 c.c. of glacial acetic acid. This hemolyzes the red blood cells but fixes neoplastic and other nucleated cells without distortion. There is, however, a tendency for the cells in certain cases to stain less vividly after the acid treatment. An alternate method of hemolyzing the red blood cells in aspirated fluids is the addition of the acetic acid before centrifugation; 50 per cent acetic acid is added to the fluid using about 1/20 the volume of the fluid to be examined or enough acetic acid to give complete hemolysis in about five minutes. In the case presented below, although all three methods were used the latter proved most successful.

After fixation the slides are stained for two minutes in Shorr's single differential stain, dehydrated by dipping 10 times in 80 per cent and 95 per cent alcohol, cleared in xylol, and mounted in damar with a cover slip as described by Shorr. Although the technic was originally developed for use with vaginal smears, because of the sharp differentiation given between cornified and non-cornified cells, we have found that this particular formula of Shorr's stain is an excellent nuclear stain and much more delicate than the hematoxylin-eosin stains. As the stain is a mixture of four acid dyes (Biebrich scarlet, orange G, fast green, and aniline blue) it affords no information as to the degree of acidophilia or basophilia. The cytoplasm stains green to green-blue in non-keratinized cells and specifically pink with the Biebrich scarlet in keratinized cells. Younger cells and those having apparently increased metabolic activity stain more deeply. The chromatin of the nuclei stains red-brown and may be quite dark while the nucleoli when present usually take on a translucent deep red or more rarely an olive green color.

Among the cells in fluids aspirated from serous cavities the mesothelial cells should first be mentioned because of their prominent nucleoli and their wide range of appearance in the presence of irritative phenomena. They may usually be differentiated from neoplastic cells because their chromatin clumps and nucleoli are smaller than those of tumor cells. In the case of sputum the morphology of the accumulated exfoliated cells in the respiratory and pharyngeal secretions is at first confusing, but there is a relative homogeneity within the various non-malignant cell groups. Against the background of pale blue stained mucus are seen the major cellular constituents of sputum: leukocytes, exfoliated squamous epithelial cells and large phagocytes. The leukocytes and epithelial cells look much the same as in vaginal smears and need no description. The phagocytes, whose oval shape and yellow-green cytoplasm are distinguishing features, contain ingested material or small vacuoles and vary considerably in size though little in chromicity; they are often bi- or tri-nucleate with one or two nucleoli. Other non-malignant cells which may be identified are ciliated columnar epithelial cells and metaplastic squamous cells.

Malignant neoplastic cells appear as atypical cells showing distortions of shape, variation in chromicity and certain other characteristics by which they may usually be identified. The cytoplasm often shows faint concentric rings, vacuoles, perinuclear paling, or in large cells a dark green perinuclear ring. There are marked variations in the nuclear-cytoplasmic ratio; the nuclei are often large with large irregular nucleoli. There is a tendency toward clumping of the chromatin and toward what appears to be the fusion of several nucleoli. The chromatin associated with the nucleolus usually is more dense than in non-malignant cells. The cells may appear singly or in small syncytial groups. Occasional extremely bizarre forms are encountered which reflect the exuberant growth of the neoplasm and present no trouble as to their identity.

The diagnosis of cancer depends, however, not upon finding a single pathognomonic cell but on finding many of them or on finding several small clusters of them. Caution must be observed in making a diagnosis of cancer in the presence of chronic inflammation and metaplasia since confusion may arise between "borderline" cancer cells and non-neoplastic atypical cells. This same difficulty, of course, is encountered in tissue sections.

Case Report

A 61 year old white man was admitted to the Albany Hospital on August 24, 1946. Four months previously he had coughed up thick, bright red sputum which was followed by intermittent dull right chest pain radiating to the scapula, increasingly productive morning cough, anorexia, weakness, epigastric fullness, and a 30 pound weight loss. The urge to cough was increased when lying down and, just before admission, was productive of about two ounces of sputum daily.

Past medical history revealed a gonorrheal infection as a youth and hoarseness for 35 years following "influenza."

On physical examination the blood pressure was 108 mm. Hg systolic and 70 mm. diastolic, pulse 80, respirations 24, temperature 100.4° F. The patient was a well developed white male in no acute distress, but showing signs of recent weight loss. His voice was very hoarse. There were a few telangiectases on the cheeks and thorax. No lymphadenopathy was noted. The trachea was in the midline. The chest was emphysematous but symmetrical. The lungs were resonant to percussion but inspiratory wheezes and rhonchi, as well as râles and bronchovesicular breath sounds, were heard over the right upper chest anteriorly and posteriorly. The wheeze was heard best anteriorly. The heart was not enlarged, showed normal sinus rhythm and no murmurs or friction rub. Examination of the abdomen revealed only that the liver was palpable on deep inspiration. Rectal examination was not remarkable.

Neurological examination was entirely within normal limits.

Examination of the blood showed 13 gm. hemoglobin, 4,200,000 red blood cells and 7000 white blood cells with a differential count of 86 per cent polymorphonuclear cells, 9 per cent lymphocytes, 4 per cent monocytes, and 1 per cent eosinophiles. Nonprotein nitrogen was 34 mg. per cent. Blood Wassermann test was negative. Urinalysis was not remarkable. Eight sputum examinations were performed, one of which was reported as showing a single tubercle bacillus. *Streptococcus viridans* was cultured from the sputum. Chest roentgenograms on admission showed a large cavity occupying the upper lobe of the right lung. The pleura along the axillary portion of the chest and in the interlobar fissure was thickened. There was a fluid level in the cavity.

The patient was given postural drainage and aerosol penicillin inhalations, 30,000 units every three hours throughout his hospitalization with resultant reduction of the sputum from 55 gm. to 25 gm. daily.

On August 30, bronchoscopy was performed and all the bronchi appeared normal. Secretions aspirated at bronchoscopy were sent to the pathological laboratory where no tumor cells were found in preparations stained with hematoxylin and eosin.

Electrocardiogram taken on September 16 showed left axis deviation associated with evidence of heart muscle damage probably on the basis of arteriosclerosis (low slurred R_1, slightly elevated ST_1, low T_1, slurred $QRS_{2 \text{ and } 3}$, low R_4 and depressed ST_4).

The patient felt unimproved and one month after admission began to complain of intermittent pain in both arms as well as the chest. On October 1, hyperactive right knee and ankle jerks, with slight weakness of the right arm and leg, were found. The heart sounds were very distant; no murmurs or friction rub were heard. Blood pres-

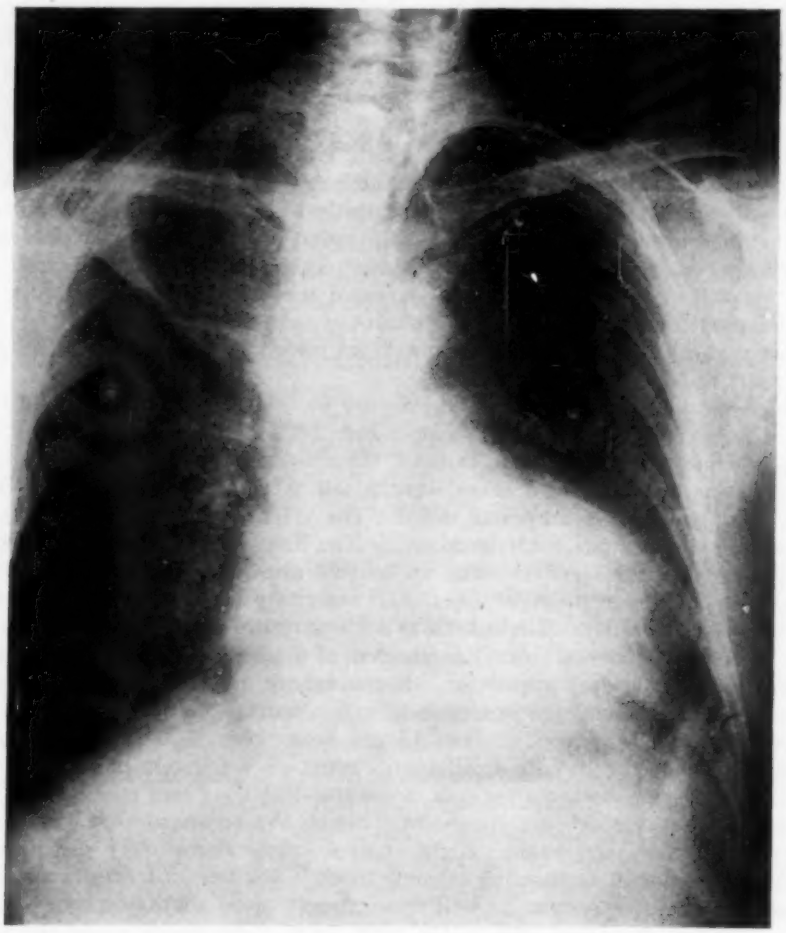

FIG. 1. Anterior-posterior roentgenogram of the chest taken October 2 showing enlargement of the heart shadow, obliteration of the left costophrenic angle, and the thickened interlobar fissure on the right. The cavity in the right upper lobe is poorly defined.

sure was 120/70, pulse 80, respirations 20. One plus pitting pretibial edema was noted. Chest roentgenograms at this time (October 2) showed fluid in the left pleural cavity and enlargement of the heart shadow (figure 1). Fluoroscopy revealed diminished pulsations particularly in the left ventricular segment of the cardiac contour. Electrocardiogram taken at the same time was described as showing increase in heart muscle damage due either to an anterior wall infarction or a pericardial effusion. (R_1 was seen to be lower and thicker, T_1 diphasic and lower, ST_1 more elevated, Q_3 more shallow (3 mm. in depth) and slurred, and T_4 diphasic.) Lumbar puncture performed because of the reflex changes gave normal chemical and cytological findings.

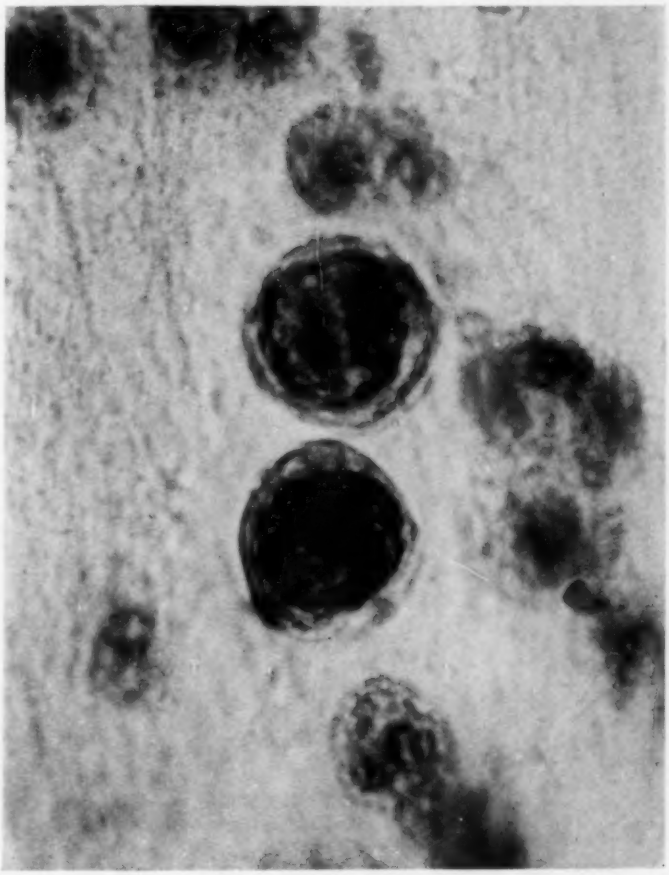

FIG. 2. Two cancer cells, sputum smear (Shorr's stain). Note the concentric irregular refractile rings in the cytoplasm, the increase in the nuclear cytoplasmic ratio, the coarse chromatin clumping, the large irregularly shaped nucleoli. × 1650.

On October 1, a sputum was submitted to one of us (F. D. McC.) for smear and examination. This revealed many atypical cells, singly and in small groups, that showed marked variation in size and density of both cytoplasm and nucleus; a few of these atypical cells were keratinized. There were many cells with large, irregular nuclei with one or more large nucleoli. The chromatin of these nuclei showed

moderate clumping and stained brown to black in contrast to the red-brown nuclei of the normal cells (figures 2 and 3). On the basis of these findings a diagnosis of bronchogenic epidermoid carcinoma was made.

On October 7, because the patient complained of increasing dyspnea and epigastric fullness and because a paradoxical pulse, a blood pressure of 100/78, and distant heart sounds were now found, a pericardial tap was performed. The pericardium was entered at the fifth left interspace in the anterior axillary line and yielded 250 c.c. of bloody non-clotting fluid with slight relief of the patient's discomfort. Further peri-

FIG. 3. A cancer cell, sputum smear (Shorr's stain). Note the irregularly folded nucleus with the surrounding ring of dark staining cytoplasm and the dense clumping of the chromatin about the nucleolus. × 1650.

cardial taps were performed on October 17 and 23, yielding 200 c.c. and 300 c.c. of bloody fluid respectively. The tap done on October 23 was performed by entering the pericardium from below by inserting the needle just to the left of the xiphoid because all attempts to enter the pericardial space by the previous route now failed. No tubercle bacilli were found in the pericardial fluid.

At the time of each pericardial tap about 15 c.c. of fluid were submitted for examination by our method, the rest being sent to the pathological laboratory where

it was spun down for cell block study (hematoxylin and eosin stain). Of the cell block studies those of the first two specimens were said to show no tumor cells while those of the third showed cells which were considered to be malignant but of unknown origin. However, in all three specimens of pericardial fluid smeared and stained with Shorr's stain atypical cells were found, many of which were identical with the non-keratinized cells seen in the sputum and confirmed the now suspected diagnosis of bronchogenic epidermoid carcinoma metastatic to the pericardium (figures 4 and 5).

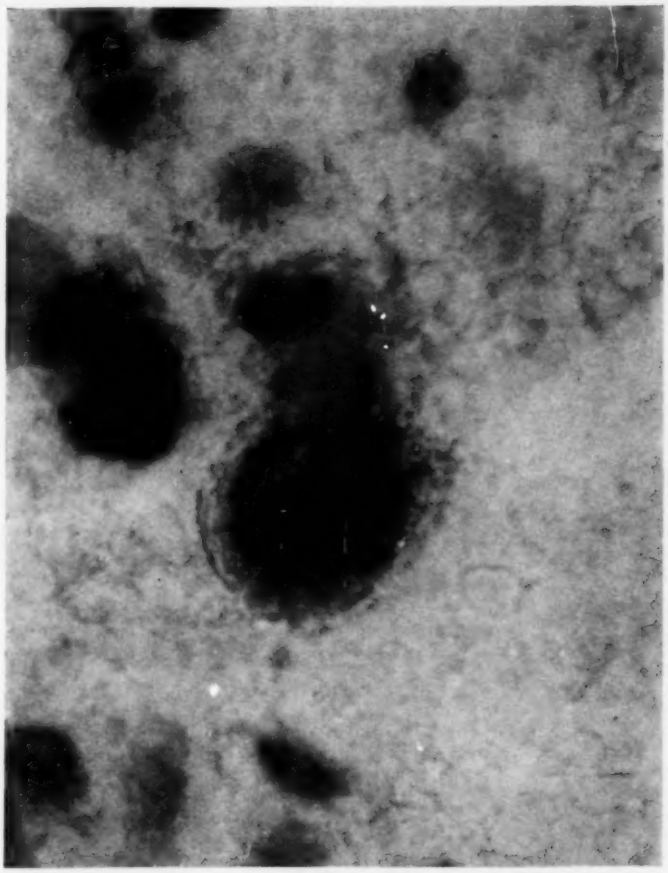

FIG. 4. A cancer cell from a smear of the pericardial fluid withdrawn on October 7 (Shorr's stain). × 1650.

The patient's subsequent course was rapidly downward. He developed venous distention and edema of the upper extremities, severe pain in the right arm, marked dyspnea, and cyanosis. Death occurred on October 28, 1946.

At necropsy the upper lobe of the right lung was found to be adherent to the chest wall. There were 1500 c.c. of dark brown fluid in the left pleural cavity and 1000 c.c. in the right. The contents of the mediastinum were normally disposed but were obscured by the presence of much firm fibrous tissue, firm gray tumor nodules, and enlarged lymph nodes. The pericardial cavity was almost completely obliterated by

invasion with tumor tissue. Both cardiac ventricles were hypertrophied, particularly the right, and the tumor was seen to have invaded the myocardium of the right ventricle. The right auricle was contracted due to invasion of the superior vena cava which was itself completely occluded by the new growth. While the aorta was surrounded by tumor tissue the intima was not invaded. The right lung showed extensive scattering of tumor nodules over the pleural surface; the two lower lobes were firm and non-crepitant and the upper lobe was found to consist almost entirely of a large cavity surrounded by tumor tissue which appeared to originate in the right upper lobe bronchus at its junction with the right main bronchus. The left lung also showed

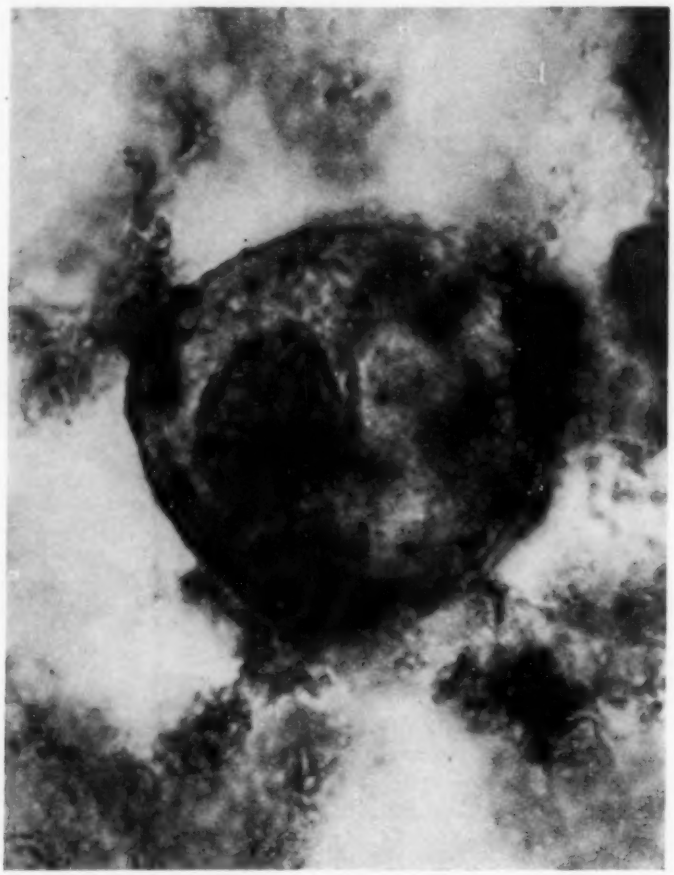

FIG. 5. A cancer cell from a smear of the pericardial fluid withdrawn on October 23 (Shorr's stain). × 1650.

some seeding of tumor as well as a confluent lobular pneumonia and chronic passive congestion. Microscopic examination of all these tissues showed invasion by squamous cell carcinomatous tissue with a disorderly pattern. The neoplasm, which showed a slight tendency toward keratinization, contained cells of varying degrees of anaplasia and degeneration. The inner surface of the cavity was found to be composed of wildly growing neoplastic epithelium. The lymphatics, including those of the esophagus, contained neoplastic emboli. No metastases were found in the brain,

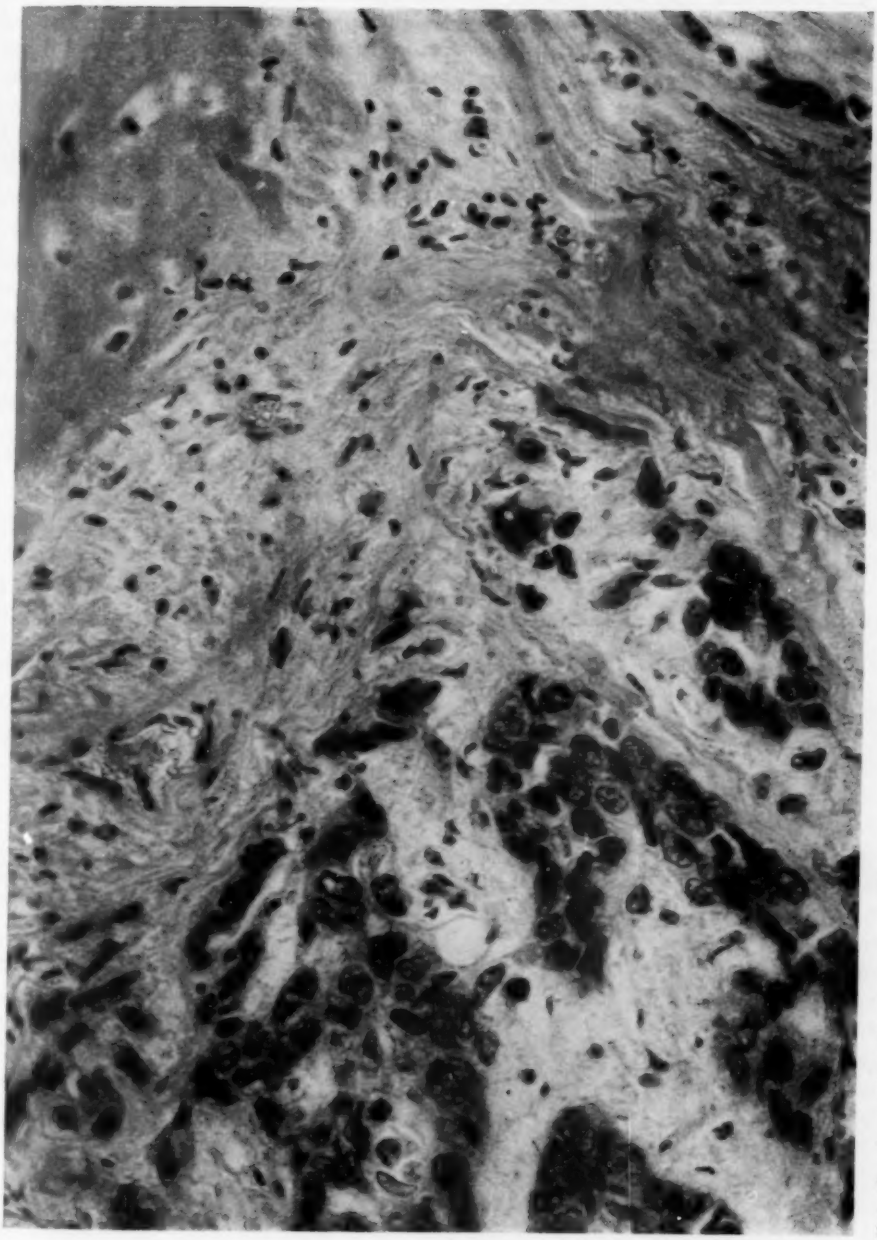

FIG. 6. A section of the tumor taken at autopsy from its origin in the right upper lobe (hematoxylin-eosin). × 375.

and the neurological findings were never explained. There was chronic passive congestion of the liver.

The anatomical diagnoses were: 1. Bronchogenic carcinoma, squamous cell type, at junction of the right main bronchus and right upper bronchus with cavitation of right upper lobe and metastases to the mediastinal lymph nodes, pleura, pericardium, and esophagus. 2. Pericarditis, adhesive, due to diffuse carcinomatosis. 3. Obstruction, mechanical, of the superior vena cava by pericardial carcinomatosis. 4. Lobular pneumonia, acute, of the lower lobes of the lungs. 5. Congestion, acute and chronic of the lungs. 6. Hydrothorax, massive, bilateral. 7. Chronic passive congestion of the liver, moderate (figures 6 and 7).

FIG. 7. The contents of the thoracic cavity, posterior view, showing the primary lesion in the right upper lobe bronchus, the cavity distal to the tumor, metastatic tumor in the lymph nodes, and metastatic tumor in the heart and pericardium with almost complete obliteration of the pericardial space.

Comment

The current increasing interest in simple, accurate, cytological technics for the diagnosis of malignancy that has been stimulated by the work of Papanicolaou and Traut,[8, 9] Meigs,[10] Herbut and Clerf,[11] and others, has presented the clinician with a valuable tool. The technic used here differs from that used by the workers above, in that Shorr's stain is a single stain and the staining of the nuclei is accomplished not by the traditional hematoxylin but by the action of a single mixture of acid dyes. This gives a nuclear stain that is much more delicate than hematoxylin and shows nuclear detail to advantage. Color contrast is good and allows the investigator to pick out atypical cells and nuclei easily with low power lenses. The disadvantage of poor staining on thick smears or in the presence of very viscid mucus, is overcome by experience in spreading the smears, by longer fixation, and by making multiple smears, usually five of each specimen. Furthermore, the method does not require extensive laboratory facilities. It saves time in staining and mounting, reducing these procedures to approximately five minutes.

So useful a supplementary tool as the smear technic may be invaluable in cases such as the one just presented where, until the sputum was examined, tuberculosis and infected pulmonary cyst were the most strongly considered diagnoses because of the roentgen-ray findings and the negative bronchoscopy. Furthermore, the exact etiology of the pericardial effusion would not otherwise have been demonstrated until necropsy. It must be remembered, however, although there is as yet no substitute for biopsy, that at times roentgen-ray may be misleading, bronchoscopy inconclusive, and biopsy unobtainable. As a result the smear technic is the only diagnostic aid available.

The reasons for the infrequency of a definite antemortem diagnosis of metastatic tumor of the heart and pericardium are two-fold: (1) Biopsy of the myocardium or pericardium is not a practical procedure. One is therefore reduced to the examination of exfoliated cells in aspirated pericardial fluid. These cells may be studied by a number of methods; the most frequently used are either the examination of stained sections of fixed embedded blocks of the cellular sediment of the fluid or stained smears of the sediment made by technics such as that described above. The relative accuracy of cell blocks and smears is not yet settled [5, 9, 12, 13] though we follow Papanicolaou in preferring the latter. In either case, one is deprived of the opportunity of examining by histological methods large masses of cells in their relationships to associated structures, but must depend upon the cytological characteristics of a relatively few detached cells for an evaluation of the pathological processes involved. The identification of malignant cells without the usual criteria of the tissue pathologist may therefore be difficult, and diagnostic accuracy will vary, not only with the method used but with the investigator.

(2) Clinical signs of pericardial disease are often absent or overlooked in those patients with known or suspected cancer of other organs who prove at autopsy to have cardiac metastases. Even when an attempt is made to study patients with both cardiac and neoplastic disease, the amount of pericardial fluid may be too small to detect by physical examination or roentgen-ray. For example, Scott and Garvin [1] in 118 cases of metastatic tumor of the heart and pericardium found involvement of the pericardium in 83 cases (70 per cent) at au-

topsy. Despite the high percentage of pericardial involvement, in only 29 cases (22 per cent) was there present acute pericardial disease that might theoretically have led to the detection during life of metastasis by a method such as ours. Similar findings are seen in the reports of Heniger,[4] Yater,[14] Helwig,[15] Pallia and Gogol[16] and others. Nevertheless, the finding of pericardial effusion is an important diagnostic sign and it would therefore appear advisable to scrutinize all cases of malignancy with any cardiac or pulmonary symptoms more critically and to utilize more carefully the cytological technics at hand.

SUMMARY

A case of bronchogenic carcinoma with metastases to the pericardium in which neoplastic cells were found in the pericardial fluid as well as in the sputum by wet films stained with Shorr's stain has been presented. The possibilities and advantages of this diagnostic technic have been discussed.

The authors wish to express their appreciation of the valuable assistance extended to them in this study by Dr. Arthur W. Wright, Professor of Pathology and Bacteriology, and by Dr. L. W. Gorham, Professor of Medicine in the Albany Medical College.

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EDITORIAL

FURTHER REFINEMENT OF LIVER EXTRACTS EFFECTIVE IN PERNICIOUS ANEMIA

THE production of liver extracts which could be administered parenterally to patients with pernicious anemia constituted an important advance in the treatment of this disease. The earlier types of extracts were crude mixtures in which the active substance was present in relatively high dilution. Although the intensive work carried on during the past 1·5 years has resulted in the production of extracts for therapeutic use of far higher concentration, attempts to isolate the active substance and determine its chemical nature have hitherto been unsuccessful. Such work has been greatly hampered by the lack of any chemical or biological test to assay or even demonstrate the active substance in the fractions being studied. This could be accomplished only by administering the material to untreated patients with pernicious anemia (or a related anemia), and the supply of suitable patients has been entirely inadequate to meet the demand.

There is now evidence suggesting that this lack may have been supplied. As the result of a systematic search for a bacterium which could be used for the microbiological assay of a factor in liver needed for growth in rats, Shorb[1] discovered that *Lactobacillus lactis* Dorner when cultivated in a suitable basal medium fulfilled this need and grew when liver or liver extract was added to the medium. When assays of various commercial liver extracts were carried out by determining the minimum quantity which would support growth, Shorb found that their activity in this respect corresponded directly and very closely to their potency in "units" as determined by therapeutic tests in patients with pernicious anemia. Shorb suggested that this LLD factor may be the therapeutically active principle in the extracts.

This procedure, therefore, seems to offer a valuable practical means of detecting and measuring—at least tentatively—the active substance in various fractions derived from liver extracts. Rickes et al.[2] have utilized this procedure in their attempts further to concentrate and isolate the active substance in these extracts.

These investigators[2] have recently reported obtaining in minute amounts a highly active crystalline substance in the form of small red needles, which they have tentatively designated as vitamin B_{12}, a term which is noncommittal as to its chemical structure and biological and therapeutic significance. Shorb[3] found that 0.000013 micrograms per ml. (1.3 parts per 100,000,000,000) sufficed to produce half maximal growth of *L. lactis* in a 23 hour growth period. With respect to weight it was 11,000 times as potent as an

[1] SHORB, M. S.: Unidentified growth factors for *Lactobacillus lactis* in refined liver extracts, Jr. Biol. Chem., 1947, clxix, 455–456.

[2] RICKES, E. L., et al.: Crystalline vitamin B_{12}, Science, 1948, cvii, 396–397.

[3] SHORB, M. S.: Activity of vitamin B_{12} for the growth of *Lactobacillus lactis*, Science, 1948, cvii, 397–398.

arbitrarily selected standard liver extract. Shorb believes that it is "either wholly or partly responsible for the LLD growth activity observed for liver extracts."

West [4] has reported the immediate results obtained by administering vitamin B_{12} to three patients with pernicious anemia in relapse in single doses of 3, 6, and 150 micrograms respectively. In all three a positive hematological response was obtained. (The response appears excellent for the larger dose but suboptimal for the smaller ones.) On the basis of these observations and microbiological assays, Rickes et al. estimated that 1 microgram of vitamin B_{12} corresponds in potency approximately to 1 U.S.P. unit of liver extract.

The therapeutic effectiveness of vitamin B_{12} has been confirmed on a limited scale by other observers. Spies et al.[5] treated two cases of pernicious anemia, two of nutritional macrocytic anemia and one of nontropical sprue; and two cases of tropical sprue in Havana [6] with single doses of 6 or 8 micrograms (one patient with pernicious anemia received 15 micrograms). In all seven cases there was a well marked reticulocyte crisis and a significant rise in hemoglobin and red cell count during a period of observation of 10 or 14 days. There was also a marked subjective improvement evident by the third to the fifth day. There was an increased feeling of well being, greater strength and vigor and mental alertness, and relief of the burning and soreness in the mouth. There was also some improvement of the diarrhea in the cases of sprue.

Spies et al.[7] have also reported similar results in the treatment of five cases of tropical sprue in Puerto Rico. One patient showed little or no response to a single dose of 4 micrograms but later responded well to a folic acid preparation. The other four after an initial dose of 10 to 25 micrograms showed a well marked hematological response together with clinical improvement, but they tended to relapse after about three weeks. The administration of second and third doses of 25 micrograms at such intervals was followed by a sharp peak in the reticulocyte count and by further hematological and clinical improvement which was well maintained in the three cases receiving three such doses. Spies estimated that a single dose of 100 micrograms would be required to get a maximum hematological response in severely ill patients. This corresponds approximately in potency to the amount of liver extract commonly administered during the first week of intensive treatment to patients severely ill with pernicious anemia.

The response of the neurological disturbances in patients with pernicious anemia to vitamin B_{12} is of great theoretical as well as practical interest. As

[4] West, R.: Activity of vitamin B_{12} in Addisonian pernicious anemia, Science, 1948, cvii, 398.

[5] Spies, T. D., et al.: Observations on the antianemic properties of vitamin B_{12}, South. Med. Jr., 1948, xli, 522–523.

[6] Spies, T. D., et al.: Observations on the hemopoietic response of persons with tropical sprue to vitamin B_{12}, South. Med. Jr., 1948, xli, 523–525.

[7] Spies, T. D., and Suarez, R. M.: Response of tropical sprue to vitamin B_{12}, Blood, 1948, iii, 1213–1220.

is well known, the lack of parallelism between the severity of the anemia and the neurological degenerations and the relative resistance of the latter to treatment have led to the suggestion that these disturbances result from different deficiencies. The view that the substances which are deficient are different, or at least that the mechanisms for maintaining the integrity of the two tissues are different, is supported by recent experiences with pteroylglutamic (folic) acid. Although the latter usually induces an excellent hematological remission and maintains the blood at essentially normal levels, at least for several months, it has failed completely to control the neurological disturbances. There is even some suggestive evidence that in large doses it may be positively harmful.[8]

The evidence now available, although scanty, indicates that vitamin B_{12} is effective in controlling the neurological disturbances as well as the anemia. Spies et al.[5, 9] reported "remarkable improvement" subjectively in the neurological disturbances of three cases of pernicious anemia given a single injection of 15 micrograms, with relief of pain, tingling, numbness and stiffness, and increased ability to walk. In one patient there was substantial improvement in the physical signs also. Berk et al.[10] have also reported marked subjective and objective improvement in the neurological disturbances in a patient in severe relapse while on inadequate treatment with pteroylglutamic acid, which had been substituted for liver extract because of severe allergic reactions to the latter. After eight daily doses of 5 micrograms had resulted in marked improvement, treatment was stopped, but within a week a regression occurred. This was again controlled promptly and further improvement initiated by resumption of treatment (5 micrograms three times a week). It is interesting that no allergic reaction occurred to these injections, although the patient still reacted strongly to ordinary liver extracts.

This evidence, although obviously scanty, is so clear cut that it strongly suggests that a deficiency of vitamin B_{12} "is closely related to the natural origin of both the blood and the nervous changes."[10] A deficiency of pteroylglutamic acid would appear to play at most a subsidiary rôle in the pathogenesis of the disease as a whole.

The chemical structure of vitamin B_{12} has not been reported. The only evidence that it is a specific individual chemical compound, aside from its extraordinary potency, is its isolation in characteristic crystalline form. The mechanism of its action in the body and its relation to other hematopoietic principles are not known, but its isolation marks a major advance and an essential preliminary step toward the elucidation of these problems. The need of vitamin B_{12} as a growth factor (LLD factor) for certain bacteria

[8] Ross, J. F., et al.: The development and progression of subacute combined degeneration of the spinal cord in patients with pernicious anemia treated with synthetic pteroylglutamic (folic) acid, Blood, 1948, iii, 68–90.

[9] Spies, T. D., et al.: The association between gastric achlorhydria and subacute combined degeneration of the spinal cord, Postgrad. Med., 1948, iv, 89–95.

[10] Berk, L., et al.: Effectiveness of vitamin B_{12} in combined system disease, New England Jr. Med., 1948, ccxxxix, 328–330.

suggests that it plays a more fundamental rôle in the physiology of living organisms than merely as a preventive of pernicious anemia.

From the practical standpoint, vitamin B_{12} has thus far been obtained only in minute amounts, and it is available only for experimental purposes and on a regrettably small scale. There is no evidence, however, and no good reason to anticipate that the therapeutic results obtained with it can not be duplicated by adequate doses of liver extracts. Neither pteroylglutamic acid nor any other material now available is an effective substitute for liver extract in the treatment of pernicious anemia.

P. W. C.

REVIEWS

The Natural History of Disease. 2nd Ed. By JOHN A. RYLE, M.A., M.D., F.R.C.P. 484 pages; 14.5 × 22.5 cm. Oxford University Press, London, New York. 1948. Price, $7.50.

Professor John Ryle is one of the giants in English Medicine. Formerly Professor of Medicine in the University of Cambridge, he was called to the bedside of King George V in consultation. He subsequently declined a knighthood. As consulting physician to Guy's Hospital, he had a large London practice, which he relinquished some years ago to accept the newly created Professorship of Social Medicine at Oxford.

His book consists of a collection of 37 papers written during the last 25 years. Three have been added since the first edition in 1936. The topics discussed are varied. Two chapters are entirely philosophical—the Physician as Naturalist, and the Hippocratic Ideal. Some, though mainly philosophical, have decided and valuable clinical bearing—Prognosis, On Nosophobia, and Diathesis or Variation and Disease in Man. In the many purely clinical papers the main territories occupied are gastro-intestinal and cardiovascular symptoms and diseases, and pyogenic infections. Many of these chapters deal with subjects of great practical importance, yet often inadequately covered by standard textbooks and clinical instructors alike—the Clinical Study of Pain, the Study of Symptoms, Observations on Colonic Pain, On Examining the Rectum, the Radial Pulse, and many others. Helpful accounts of common disorders form the subjects for other chapters, and include The Natural History of Duodenal Ulcer, Anorexia, Chronic Diarrhea and Some Alarming Seizures. The chapter on the Prognosis and Treatment of Lobar Pneumonia, despite the great advances made in this subject, has been left as it appeared in the former edition; because, in the author's words, "it would be a pity if the student were to lose interest in the prognosis and difficult judgments which it requires," and "the types of judgment requisite for assessing new methods is the same."

The book is written in simple, direct style, and is therefore easy to read. It is not a textbook in any sense. It makes no pretence to give a complete account of, or even to be up to date in the knowledge of many of the subjects discussed. It consists literally of pages from the notebook of a great clinician and a widely acclaimed teacher—"gleanings from the current experience of a general physician." The main concern of the author is the symptomatology and portraiture of disease, and little mention is made of accessory aids to diagnosis. To that breed of physicians, therefore, whose interest is focussed more on the laboratory sheet than on the patient, this book will make weary, stale and flat, though not unprofitable, reading.

In this day and country, with clinical instruction too often in the hands of young and callow physicians, whose experience is necessarily limited and judgment unformed, these pages should be of particular value to the student and interne. Even the established physician (although as he reads he may be impatient at much that appears naive or repetitious) would do well to refresh himself with the principles and value of careful, bedside observation, so well set out in these chapters, and so often overlooked in today's super-scientific enthusiasm. "No amount of scientific training or technical ability can supply those qualities of naturalist and of humanist, without which the good physician can never fully earn his title."

H. J. L. M.

Occupational Medicine and Industrial Hygiene. By RUTHERFORD T. JOHNSTONE, A.B., M.D., Consultant in Industrial Health, Los Angeles. 604 pages; 17 × 25 cm. C. V. Mosby Co., St. Louis. 1948. Price, $10.00.

This excellent book begins with a section covering miscellaneous subjects, including a short historical introduction to industrial medicine. A chapter consists of definitions and of tabulations of the compensation laws of various states. Following this there is a comprehensive discussion of the functions of an industrial surgeon with the objectives to be obtained. Next, a tabulation of laboratory procedures in the diagnosis of occupational poisoning, with normal findings when available; a very valuable summary.

Approximately one-fourth of the book is devoted to the various toxic agents used in industry. These have been given adequate consideration. The author emphasizes those which have such use by the laity that the general physician is apt to come across occasional examples of poisoning in his practice, such as methyl alcohol, carbon monoxide, carbon tetrachloride, methyl chloride and sulfur dioxide. Carbon monoxide poisoning is covered at some length, not only the usual body changes following exposure, but also the more controversial aspects as to the possibility of permanent sequelae in the central nervous system and in the heart.

The heavy metals are considered in considerable detail. In discussing lead poisoning the author is quite emphatic in stressing the necessity for accurate diagnosis, and expresses the belief that in industry many individuals are diagnosed as having lead poisoning upon insufficient grounds. Here again he points out the controversial aspects, particularly whether lead can be fixed in a stable form in the skeletal system. This was the conception of Aub, Fairhall, Minot and Reznikoff, as published in 1926. Since then the dietary treatment has been based on the use of high calcium diets to "fix the lead" and low calcium intake to "delead." The author quotes certain investigators whose work indicates that this is doubtful and indeed that a high calcium diet to deposit lead in the bones may have serious consequences.

Another one-fourth of the book takes up the changes produced by the inhalation of the various dusts including silicosis, anthrosilicosis, asbestosis, etc. as well as a so-called inert dust. These chapters are well illustrated, and afford a compact and yet informative review of this important subject. There is included a short but pertinent chapter devoted to the consideration of tuberculosis and pneumonia in industry.

The occupational dermatoses are dealt with rather briefly with emphasis given chiefly to diagnostic criteria. There are well illustrated chapters on various phases of industrial hygiene.

An appendix tabulates the numerous chemicals contained in trade-name products used in the various industries as well as by the laity. This table is especially valuable as affording information which cannot be obtained from the labels on the products themselves nor from the publications of the manufacturer.

As stated in the beginning, this is an excellent book. It seems primarily intended for the use of plant physicians and other specialists in industrial medicine. However, the informative discussions of the commoner exposures, and particularly the references appended at the end of each chapter, would make this book also serve as a quick reference for the doctor who is only occasionally interested in industrial medical problems.

G. C. L.

Psychiatry for the Pediatrician. By HALE F. SHIRLEY, M.D. 442 pages; 16 × 24 cm. The Commonwealth Fund, New York. 1948. Price, $4.50.

The very first chapter in this book introduces the general practitioner and pediatrician to many old patients. There again is Johnny, who objects to examination;

Elsie, who doesn't want to eat; James, wailing to go home and his mother who vociferously objects to waiting. And Mrs. Brown who wants to know how she can make Nancy take her afternoon nap, as well as Mrs. Black who wants to know what the doctor is going to do "next" about Henry's bed-wetting. Admittedly they are all familiar characters and problems, and here Dr. Shirley lays the pattern for subsequent discussion. The book throughout is kept at a level of presentation that is commensurate with the practitioner's knowledge of child psychiatry. As stated in the preface, it is devoid of "psychiatric verbiage," and as an aid to a more complete understanding, a short glossary has been appended. The departures made from common every day behavior problems into true psychopathological problems are infrequent and only serve to provide the practitioner with some norm as to his limitation.

There has been an increasing demand made upon the general practitioner and pediatrician to help parents emerge from the morass of confusing psychological advice that has been appearing in current lay publications. This book seems to the reviewer to be a timely publication in providing the physician with an understanding of these problems. Indeed more discussion should be allotted to the environmental factors, such as "movies," "comics," and radio with presentation of prevailing views other than the author's as to their influence upon child development.

An entire chapter is given over to the discussion of "Sexual Factors and Problems," and the discussion is on a sane, common sense level devoid of the almost pathological significance that many psychiatrists attach to this drive.

J. E. B.

Diabetes Mellitus in General Practice. By ARTHUR R. COLWELL, M.D. 350 pages; 14.5 × 21 cm. The Year Book Publishers, Inc., Chicago. 1947. Price, $5.25.

Dr. Colwell has written an interesting monograph on the treatment of diabetes. The qualification of the title by the words "In General Practice" is somewhat misleading, as the presentation is probably too detailed to appeal to the average general practitioner. The book is more suited to the use of the internist.

The subject matter is clearly presented, the general plan of treatment is good, and discussions of emergencies and complications are satisfactory. Usefulness of the book could be increased by inclusion of a large number of sample diets, as calculation of the dietary prescription is for most physicians a difficult problem.

The reviewer, who is diabetic, believes that the description of the technic of insulin administration is too complicated. He is also aghast at the suggestion that diabetes in a pregnant woman is an indication for abortion if the husband's family history is found to be positive.

With these few exceptions, "Diabetes Mellitus in General Practice" may be recommended as a satisfactory guide for the management of the diabetic patient.

T. N. C.

The Diagnosis and Treatment of Menstrual Disorders in Sterility. 2nd Ed. By CHARLES MAZER and S. LEON ISRAEL. 570 pages; 16.5 × 24 cm. Paul B. Hoeber, Inc., New York, N. Y. 1946. Price, $7.50.

This rewritten second edition, like the first, has been designed to fulfill the need of the general practitioner who is interested primarily in the practical aspects of these subjects. New developments in the field of endocrinology and the extensive clinical experience of the authors in dealing with problems of sterility made revision necessary. All but four chapters have been largely rewritten. Some have been considerably enlarged.

The book begins with a detailed description of the anatomy and physiology of the pituitary gland and the ovary. There is included in the first part a discussion of anti-

hormone effects. Also, there is an outline of the relative potency of the numerous estrogens in terms of international and rat units per milligram and the most effective methods of administration of these products. Following this there are chapters on puberty in the female, the normal menstrual cycle, and the hormone balance of the normal menstrual cycle. These add nothing new.

Dysmenorrhea, premenstrual tension, migraine, breast hyperplasia, mittelschmertz, and vicarious menstruation are dealt with in a rather elementary way, but the authors stress the essential known facts regarding the etiology and treatment of these conditions. Amenorrhea, functional bleeding, and sterility are discussed in great detail and the chapters dealing with these subjects are excellent. Methods of diagnosis, office procedures and treatment are given in detail.

The chapter on male infertility is by Dr. Charles W. Charney. It has been completely rewritten and covers the subject thoroughly. Toxemias of pregnancy and the Rh factor are discussed very briefly and might just as well have been omitted. At the end of the book there is a very excellent detailed list of the various commercially available standardized products. The book includes many excellent photographs and microphotographs.

Throughout, one cannot help but be impressed by the sincerity of the authors in their effort to stress proved, modern methods of treatment for these clinically related conditions. This book fills a gap between the ultra-scientific papers on endocrinological subjects and the "commercial propaganda" regarding the clinical use of hormones. The book is well worth reading.

J. C. D.

BOOKS RECEIVED

Books received during October are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

A. M. A. Interns' Manual. 201 pages; 18.5 × 11 cm. 1948. W. B. Saunders Company, Philadelphia. Price, $2.25.

Ärztliche Rheokardiographie. By WOLFGANG HOLZER and KURT POLZER. 141 pages; 24 × 17 cm. (paper bound). 1948. Verlag Wilhelm Maudrich, Vienna, Austria; imported by Grune & Stratton, New York. Price, $3.00.

Die Stumpfen Bauchverletzungen ihre Erkennung und Behandlung. By DR. ADALBERT SLANY. 137 pages; 23 × 15.5 cm. (paper bound). 1948. Verlag Wilhelm Maudrich, Vienna, Austria; imported by Grune & Stratton, New York. Price, $3.50.

Die Vegetativen Anfälle des Herzens. By KURT POLZER and WALTER SCHOBER. 88 pages, 23 × 15.5 cm. (paper bound). 1948. Verlag Wilhelm Maudrich, Vienna, Austria; imported by Grune & Stratton, New York. Price, $2.50.

Human Biochemistry. 2nd ed. By ISRAEL S. KLEINER, Ph.D., Professor of Biochemistry and Director of the Department of Physiology and Biochemistry, New York Medical College, Flower and Fifth Avenue Hospitals, etc. 649 pages; 25 × 17 cm. 1948. The C. V. Mosby Company, Saint Louis. Price, $7.00.

Liver Injury: Transactions of the Seventh Conference, January 15 and 16, 1948, New York, N. Y. Edited by F. W. HOFFBAUER, M.D., Department of Medicine, University of Minnesota. 95 pages; 23 × 16 cm. (looseleaf, paper bound). 1948. Josiah Macy, Jr. Foundation, New York. Price, $1.50.

Malignant Disease and Its Treatment by Radium. Volume I. 2nd Ed. By SIR STANFORD CADE, K.B.E., C.B., F.R.C.S., M.R.C.P., Surgeon, Westminster Hospital, Mount Vernon Hospital and Radium Institute, etc.; with a Foreword by SIR ERNEST ROCK CARLING, F.R.C.P., F.R.C.S., F.F.R., Consulting Surgeon and Vice-President, Westminster Hospital. 383 pages; 23.5 × 16 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, $12.50.

Management of Common Gastro-intestinal Diseases. Edited by THOMAS A. JOHNSON. Contributors: A. H. AARON, ALBERT F. R. ANDRESEN, Z. T. BERCOVITZ, J. EDWARD BERK, OLOV BLOMQUIST, E. N. COLLINS, BURRILL B. CROHN, E. GARCIA, M. I. GROSSMAN, W. PAUL HAVENS, JR., A. C. IVY, SARA M. JORDAN, JOSEPH B. KIRSNER, N. HABALUYAS KUO, ELMER MILCH, WALTER LINCOLN PALMER, RUDOLF SCHINDLER, Co TUI, HENRY J. TUMEN, EDWARD WEISS, and HARRY YARNIS. 280 pages; 24 × 16 cm. 1948. J. B. Lippincott Company, Philadelphia. Price, $7.00.

Methods in Medical Research. Volume I. VAN R. POTTER, Editor-in-Chief. Assay of Antibiotics, HENRY WELCH, Editor; Circulation—Blood Flow Measurement, HAROLD D. GREEN, Editor; Selected Methods in Gastroenterologic Research, A. C. IVY, Editor; Cellular Respiration, VAN R. POTTER, Editor. 372 pages; 23.5 × 15.5 cm. 1948. Year Book Publishers, Inc., Chicago. Price, $8.00.

Pediatrics and the Emotional Needs of the Child, as Discussed by Pediatricians and Psychiatrists at Hershey, Pennsylvania, March 6–8, 1947. Edited by HELEN L. WITMER. 180 pages; 23 × 15.5 cm. (paper bound). 1948. The Commonwealth Fund, New York. Price, $1.50.

Psychiatry in General Practice. By MELVIN W. THORNER, M.D., D.Sc., Assistant Professor of Neurology, The Graduate School of Medicine, University of Pennsylvania. 659 pages; 24 × 16 cm. 1948. W. B. Saunders Company, Philadelphia. Price, $8.00.

The RH Blood Groups and Their Clinical Effects—Medical Research Council Memorandum No. 19. By P. L. MOLLISON, A. E. MOURANT and R. R. RACE. 74 pages; 24.5 × 15 cm. (paper bound). 1948. His Majesty's Stationery Office, London. Price, 1s. 6d. net.

The Surgery of Abdominal Hernia. By GEORGE B. MAIR, M.D., F.R.F.P.S.G., F.R.C.S.E., Surgeon, Law Junction Hospital, Lanarkshire, etc. 408 pages; 22 × 14.5 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, $7.00.

The Thyroid and Its Diseases. 2nd Ed. By J. H. MEANS, M.D., Jackson Professor of Clinical Medicine, Harvard University, etc. From the Thyroid Clinic of the Massachusetts General Hospital. 571 pages; 23.5 × 15.5 cm. 1948. J. B. Lippincott Company, Philadelphia. Price, $12.00.

Über Neurome und Neurofibromatose, Nach Untersuchungen am Menschlichen Magendarmschlauch. By F. FEYRTER, O. Professor der Pathologie, Georg Hanusch-Krankenhaus der Wiener Gebietskrankenkasse für Arbeiter und Angestellte, Wien XIV. 125 pages; 24.5 × 17.5 cm. (paper bound). 1948. Verlag Wilhelm Maudrich, Vienna, Austria; imported by Grune & Stratton, New York. Price, $3.50.

Viral and Rickettsial Infections of Man. Edited by THOMAS M. RIVERS, M.D., Director of the Hospital, The Rockefeller Institute for Medical Research. 587 pages; 26.5 × 18 cm. 1948. J. B. Lippincott Company, Philadelphia. Price, $5.00.

COLLEGE NEWS NOTES

Meeting of the Board of Regents

The Board of Regents met in Philadelphia on November 7, 1948. The minutes of this meeting will be published in a later issue of the Annals of Internal Medicine.

The following candidates were elected as Fellows or Associates of the American College of Physicians.

Fellows

Edwin Bennett Astwood ..... Boston, Mass.
Oscar Auerbach ..... Staten Island, N. Y. (V. A.)
Noyes Latham Avery, Jr. ..... Grand Rapids, Mich.

Joseph Ballinger ..... New York, N. Y.
Charles Scott Barker ..... Montreal, Que., Can.
Joseph Michael Barker ..... Washington, D. C.
William Bennett Bean ..... Iowa City, Iowa
Milton Dietrick Bosse ..... Pitcairn, Pa.
J(ames) Russell Brink ..... Grand Rapids, Mich.

Mortimer Jacob Cantor ..... Brooklyn, N. Y.
David Cayer ..... Winston-Salem, N. C.
Don Wilton Chapman ..... Houston, Tex.
Aaron Cohen ..... Brooklyn, N. Y.
Peter Diacoumis Comanduras ..... Arlington, Va.
William Dean Coventry ..... Duluth, Minn.
William Llewellyn Cover ..... San Bernardino, Calif.

Joseph Henry Delaney, Sr. ..... Spokane, Wash.
Vincent Joseph Derbes ..... New Orleans, La.
Nicholas John DiGregorio ..... Brooklyn, N. Y.
Joseph Doupe ..... Winnipeg, Man., Can.

Earl Foster Evans ..... M. C., U. S. Navy

Neil Feeney ..... Montreal, Que., Can.
Marcus Abraham Feinstein ..... New York, N. Y.
Elmer Friedland ..... Buffalo, N. Y.

Arthur Joseph Geiger ..... New Haven, Conn.

Robert Hardin Hackler, Jr. ..... Washington, N. C.
Oscar Carl Edvard Hansen-Pruss ..... Durham, N. C.
Hilbert Lawrence Harris ..... Syracuse, N. Y.
Peter Andrew Herbut ..... Philadelphia, Pa.
Lawrence Wheelock Holden ..... Boulder, Colo.

Joseph Carlino Indelicato ..... Brooklyn, N. Y.

Lewis Edward January ..... Iowa City, Iowa
Sture A. M. Johnson ..... Madison, Wis.

William Henry Kammerer ..... New York, N. Y.
Max Joseph Klainer ..... Stoneham, Mass.
Yale Knefland, Jr. ..... New York, N. Y.
Israel Kopp ..... Boston, Mass.

Sprul Tul Lauffer ..... Halifax, N. S.
Edward James Lefeber ..... Galveston, Tex.
William Cohn Levin ..... Galveston, Tex.
Frederic Henry Lewey ..... Philadelphia, Pa.
Victor Filler Lief ..... Far Rockaway, N. Y.
Louis Robert Limarzi ..... Chicago, Ill.
Wallace William Lindahl ..... Seattle, Wash.
Eugene Leonard Lozner ..... Syracuse, N. Y.
Mischa J. Lustok ..... Milwaukee, Wis.

Paul Budd Magnuson ..... Washington, D. C. (V. A.)
Ronald John McNamara ..... Charleston, W. Va.
Theodore Herzl Mendell, Sr. ..... Philadelphia, Pa.
Edward Sadler Mills ..... Montreal, Que., Can.
Samuel Mirsky ..... Ottawa, Ont., Can.
Franklin David Murphy ..... Kansas City, Kan.

Don Edwin Nolan ..... Dayton, Ohio (V. A.)

Oscar Armand Palatucci ..... New York, N. Y.
Jerome Thomas Paul ..... Wilmette, Ill.
William Nottingham Powell ..... Temple, Tex.
Samuel Jeremiah Prigal ..... New York, N. Y.
Roscoe LeRoy Pullen ..... Seattle, Wash.

Joseph George Ruston, Sr. ..... Glendale, Calif.

Clement Franklin St. John ..... M. C., U. S. Army
Bertram Julian Sanger ..... New York, N. Y.
Edmund Lester Shlevin ..... Brooklyn, N. Y.
Norman Richard Shulack ..... Brooklyn, N. Y.
Leslie Benjamin Smith ..... Phoenix, Ariz.
Richard Henry Smith ..... USPHS
Mayo Hamilton Soley ..... Iowa City, Iowa
Robert Folger Solley ..... Palisades, N. Y.
Charles Lewis Spurr ..... Houston, Tex.
Irwin Daniel Stein ..... Tuckahoe, N. Y.

Robert Harold Talkov ..... Boston, Mass.
Lawrence Jay Thomas ..... Washington, D. C.

Samuel Waldman ..... Brooklyn, N. Y.
Joseph James Wallace ..... Washington, D. C.
Otis Sumter Warr ..... Memphis, Tenn.
Earle Macbeth Watson ..... London, Ont., Can.
Joseph Cook Watts ..... Bayside, N. Y.
Frederick Renfroe Weedon ..... Jamestown, N. Y.
Samuel Joseph Weinberg ..... Los Angeles, Calif.
William Hays Windley ..... Newport News, Va.

George Alexander Zindler ..... Battle Creek, Mich.

Associates

Emanuel M. Abrahamson ..... New York, N. Y.
Alan Louis Abrams ..... San Francisco, Calif.
Harry Nils Akesson ..... Oakland, Calif.

John Bellows Alsever ..... USPHS
Leighton Lars Anderson ..... Denver, Colo.
Maurice Joseph Ansfield ..... Milwaukee, Wis.

Prince Patanilla Barker ..... Tuskegee, Ala. (V. A.)
Biagio Battaglia ..... Brooklyn, N. Y.
Frank Louis Bauer ..... M. C., U. S. Army
Robert H. Beck ..... Huntingdon, Pa.
Paul Lincoln Bedinger ..... Evanston, Ill.
Virginia Patterson Beelar ..... Washington, D. C.
Nathaniel G. Berk ..... Philadelphia, Pa.
John William Berry ..... Denver, Colo.
Albert Alfred Biederman ..... M. C., U. S. Army
Olov Albert Blomquist ..... Los Angeles, Calif.
Albert Murton Bond ..... Melrose, Mass.
Katherine Helen Borkovich ..... Baltimore, Md.
Edward Thurston Brading ..... Johnson City, Tenn.
Thomas Wayne Brewer ..... Houston, Tex.
William Charles Bridges ..... Seattle, Wash.
Francis Jack Brown ..... Decatur, Ill.
Robert Hamilton Browning ..... Oberlin, Ohio
Walter Albert Brussock ..... Milwaukee, Wis.
John Myles Buchanan ..... Huntington Park, Calif. (V. A.)
Philip Larkin Byers ..... Kansas City, Mo.

Orlando Canizares ..... New York, N. Y.
David Turner Carr ..... Rochester, Minn.
William Robert Carson ..... Potsdam, N. Y.
William Arnold Christian ..... Chicago, Ill. (V. A.)
Elmer Fredolph Christopherson ..... Vancouver, B. C., Can.
John Mark Church ..... Fort Worth, Tex.
Edward Alexander Cleve ..... M. C., U. S. Army
Archibald Clinton Cohen ..... Butler, Pa. (V. A.)
Isidor Cohn ..... Brooklyn, N. Y.
Ralph Earl Cole ..... Westford, Mass.
Morris Frank Collen ..... Oakland, Calif.
James Robert Colvert ..... Oklahoma City, Okla.
William Leigh Cook, Jr. ..... Pittsburgh, Pa.
Patrick John Valentine Corcoran ..... Evansville, Ind.
Norman Leo Cressy ..... Newington, Conn. (V. A.)
Leo Hermann Criep ..... Pittsburgh, Pa.
James Hawley Currens ..... Boston, Mass.

Quin Bernard DeMarsh ..... Seattle, Wash.
Charles Campbell Derrick ..... Springfield, Mass.
Francis Curtis Dohan ..... Bala-Cynwyd, Pa.

John Newell Edson ..... Brooklyn, N. Y.
Thomas Stilwell Edwards ..... Charlottesville, Va.
Roger Olaf Egeberg ..... Los Angeles, Calif. (V. A.)
William Weborg Engstrom ..... New Haven, Conn.

Fredric Bickel Faust ..... Lansdowne, Pa.
Louis Feldman ..... Chicago, Ill.
Samuel A. Feldman ..... New York, N. Y.
Leonard Elihu Field ..... New York, N. Y.

Morris Fogel ..... Brooklyn, N. Y.
George William Forman ..... St. Joseph, Mo.
John Franklin ..... Norfolk, Va.
Arthur J. Freedman ..... Greensboro, N. C.
Robert John Freedman ..... Alexandria, La. (V. A.)
Rudolph Eric Fremont ..... Staten Island, N. Y. (V. A.)
Robert Friedenberg ..... Albuquerque, N. M.
Sidney Friedlaender ..... Detroit, Mich.
Joseph Harman Fries ..... Brooklyn, N. Y.
Andrew Bole Fuller ..... Pittsburgh, Pa.

H(enry) Harold Gelfand ..... New York, N. Y.
Alexander Gerber ..... Brooklyn, N. Y.
Horace Craig Gibson ..... M. C., U. S. Army
William Carleton Gibson ..... Edmonton, Alta., Can. (Temporarily in Australia)
James Samuel Glotfelty ..... St. Louis, Mo. (V. A.)
Herman Gold ..... Chester, Pa.
Morris Alan Gold ..... Butte, Mont.
Emanuel Goldberger ..... New York, N. Y.
Mervin Jack Goldman ..... San Francisco, Calif. (V. A.)
Robert Sid Arthur Green ..... Cincinnati, Ohio
Lucien Anthony Gregg ..... Pittsburgh, Pa.
Elizabeth Grimm ..... Madison, Wis.
Marshall Eugene Groover, Jr. ..... M. C., U. S. Army
Stanley Herbert Gumbiner ..... Chicago, Ill.

Robert Calvin Hardin ..... Iowa City, Iowa
Max Harten ..... Brooklyn, N. Y.
Edgar A. Haunz ..... Grand Forks, N. D.
William Isaac Heine ..... Philadelphia, Pa.
Robert Arthur Hettig ..... Houston, Tex.
Ralph Emerson Hibbs ..... Portland, Ore.
Homer Allen Howes ..... Detroit, Mich.
Ferdinand Joseph Henry Hruby ..... Cleveland, Ohio
Leroy Hyde ..... Van Nuys, Calif. (V. A.)

Grover Donald Icenogle ..... Bismarck, N. D.

Harold Melvin Johnson ..... Honolulu, T. H.
Reverdy Hamlin Jones, Jr. ..... Roanoke, Va.
Cheney Cleveland Joseph ..... Baton Rouge, La.

Gustav Mason Kahn ..... M. C., U. S. Navy
Julius Kahn ..... Beverly Hills, Calif.
Aaron Louis Kaminsky ..... M. C., U. S. Army
Milton Kantor ..... Mountain Home, Tenn. (V. A.)
Hyman Mandel Katz ..... Brooklyn, N. Y. (V. A.)
Eugene Maurice Katzin ..... Newark, N. J.
Manuel Kaufman ..... Boston, Mass.
Walter Kempner ..... Durham, N. C.
Winfred Price Killingsworth ..... Port Arthur, Tex.
Friedrich Wilhelm Klemperer ..... Trudeau, N. Y.
Joseph Francis Kuzma ..... Wauwatosa, Wis.

Robert (Evariste) Lachance ..... Verdun, Que., Can.
Aaron Melchior Lefkovits ..... Memphis, Tenn. (V. A.)
Jack Jay Levin ..... Wood, Wis. (V. A.)
Dexter Shirley Levy ..... Buffalo, N. Y.
Max(well) Peter Lipman ..... Los Angeles, Calif.
Bernard M. Lipschultz ..... Dallas, Tex. (V. A.)
Ephraim Theodore Lisansky ..... Baltimore, Md.
David Littmann ..... West Medford, Mass. (V. A.)
Harold Joseph Livingston ..... Brooklyn, N. Y.
William Pierce Logan ..... Lakeland, Fla.
Robert Stanley Long ..... Omaha, Nebr.
Leonard Louis Lovshin ..... Shaker Heights, Ohio
Hope Lowry ..... Denver, Colo.
Harold Duff Lynch ..... Evansville, Ind.
Benjamin Harry Lyons ..... Winnipeg, Man., Can.

Harold Joseph Magnuson ..... USPHS
Florence Iris Mahoney ..... Memphis, Tenn. (V. A.)
Philip Wallace Mallory ..... M. C., U. S. Army
Joseph Pickett McCracken ..... Durham, N. C.
Clinton Hull McKay ..... Charlotte, N. C.
Atholl Munro McNabb ..... Ottawa, Ont., Can.
Donald Lauchlin McNeil ..... Calgary, Alta., Can.
Joseph Goheen McWilliams ..... Providence, R. I.
Manson Meads ..... Winston-Salem, N. C.
Walter Herman Mendel ..... Memphis, Tenn. (V. A.)
John Kimberly Meneely, Jr. ..... Albany, N. Y.
Donald Duncan Meyer ..... Potwin, Kans.
Hyman Miller ..... Beverly Hills, Calif.
Robert Francis Miller ..... Portland, Ore.
Clark Herold Millikan ..... Iowa City, Iowa
Sidney Pearce Mitchell ..... Palo Alto, Calif.
Maurice Roberts Moore ..... Norwich, Conn.
Jacob Copple Moscovich ..... West Vancouver, B. C., Can.
Harold Krieger Moss ..... Cincinnati, Ohio
Earnest Eric Muirhead ..... Dallas, Tex.
Earl I. Mulmed ..... Tulsa, Okla.
Colin Alexander Munroe ..... Charlotte, N. C.

David Aaron Nathan ..... Miami Beach, Fla.
George Loren Norris ..... Winfield, Kans.

John Wendell Oast, III ..... Norfolk, Va.
Jacques Olivier ..... Sherbrooke, Que., Can.
Oscar Charles Olson ..... Spokane, Wash.
William Emanuel Olson ..... Fort Meade, S. D. (V. A.)
Elliot Oppenheim ..... New York, N. Y.
Arthur Hazleton Owens, Jr. ..... Birmingham, Ala.

Franklin Kittredge Paddock ..... Pittsfield, Mass.
Jean Peter Papps ..... Forest Hills, N. Y.
Benjamin Pearlman ..... Chicago, Ill.
Clarence Coplyn Pearson ..... Seattle, Wash.
Martin Perlmutter ..... Brooklyn, N. Y.
John Eric Peterson ..... Los Angeles, Calif.

David Chester Pewterbaugh ..... York, Pa.
Gerald Irving Pitegoff ..... Hartford, Conn.
William Rady Platt ..... Louisville, Ky.
Theodore Zane Polley ..... Joliet, Ill.
Byron Edward Pollock ..... M. C., U. S. Army
Clifford Porter Powell ..... M. C., U. S. Navy
Curtis Prout ..... Dedham, Mass.

Adolph Post Raab ..... Brooklyn, N. Y.
Carl Hirsch Rabin ..... New Orleans, La.
Linus Edwin Rausch ..... Dayton, Ohio
Jerome Olkin Ravel ..... Austin, Tex.
John Thomas Read ..... Columbus, Ohio
William Earl Redfern ..... Detroit, Mich.
Roy Foster Roberts ..... M. C., U. S. Army
Edward Heinrich Robitzek ..... Staten Island, N. Y.
Jack Morton Rose ..... Houston, Tex.
Reno Rosi ..... Chicago, Ill.
Bernard Daniel Ross ..... Miami, Fla.
William Rottersman ..... North Little Rock, Ark. (V. A.)

Ernest Welton Saward, Jr. ..... Vancouver, Wash.
Harold Scheff ..... St. Louis, Mo.
Isadore Schlamowitz ..... Brooklyn, N. Y.
Edward David Schwartz ..... Cleveland, Ohio
Harold Schwartz ..... Cleveland Heights, Ohio (V. A.)
I(sidor) Richard Schwartz ..... Brooklyn, N. Y.
Nathaniel H. Schwartz ..... Port Chester, N. Y.
David William Scott, Jr. ..... Fredericksburg, Va.
Sydney Selesnick ..... Newington, Conn. (V. A.)
Thomas Richard Shoupe ..... Findlay, Ohio
Warren Kousch Simmons ..... Rhinelander, Wis.
Ethan Allen Hitchcock Sims ..... New Haven, Conn.
Joseph Slusky ..... Detroit, Mich.
Harald Aasvald Smedal ..... M. C., U. S. Navy
Donal Ross Sparkman ..... Seattle, Wash.
Paul William Spear ..... Brooklyn, N. Y. (V. A.)
Tobias Stein ..... Boston, Mass. (V. A.)

John Henry Taber ..... M. C., U. S. Army
Alex(ander) Watkins Terrell, Jr. ..... Dallas, Tex.
T(homas) Ewing Thompson, Jr. ..... Pittsburgh, Pa.
Stephen Benedict Thorson ..... Calgary, Alta., Can.
Paul Kinley Tisdale ..... St. Vital, Man., Can.
Charles Robert Tittle, Jr. ..... Glenside, Pa.
George Joseph Train ..... Brooklyn, N. Y.

George Panages Vryonis ..... Alexandria, La. (V. A.)

Ephraim Lionel Wagner ..... Houston, Tex.
Harry C. Wall ..... Kansas City, Mo.
Norman Melvin Wall ..... Pittsburgh, Pa.
David Michael Wayne ..... Fort Meade, S. D. (V. A.)
Frederick Clarence Weber, Jr. ..... Greenwich, Conn.
Charles Randall Welfare ..... Winston-Salem, N. C.

Benjamin Baxter Wells ..... Houston, Tex.
John Henry Wheeler ..... Kansas City, Mo.
J(oseph) Maxwell Williams, Jr. ..... Tampa, Fla.
Norman Eric Williams ..... Daytona Beach, Fla.
Onie Owen Williams ..... Phoenix, Ariz.
Marvin Norman Winer ..... Buffalo, N. Y.
Jack Walter Wolf ..... Kansas City, Mo.
Harris Lincoln Woodburne ..... Detroit, Mich.

Cyril Thompson Yancey ..... Monroe, La.

Henry A. Zimmerman ..... Cleveland, Ohio
Lynwood Duane Zinn ..... Clarksburg, W. Va.
Irving Herman Zitman ..... Chicago, Ill.

Award of Research Fellowships

The Board of Regents of the College awarded eight Research Fellowships in Medicine for the year beginning July, 1949, to applicants nominated by the Committee on Fellowships and Awards. The Fellowships are designed especially for the benefit of young physicians who are in the early stages of preparation for a teaching and investigative career in medicine. As in past years, there were many applications to be studied by the members of the Committee.

The awards for 1949–1950 were made to the foliowing physicians:

James Kilgore DeVore, M.D., of Dallas, Tex. A graduate of Central College, Fayette, Mo., in 1943, Dr. DeVore received the M.D. degree from the University of Oklahoma School of Medicine in 1947, and interned at the State of Wisconsin General Hospital, Madison, in 1947–1948. Now a fellow in internal medicine in The Frank E. Bunts Education Institute of the Cleveland Clinic, Dr. DeVore will conduct studies next year with Drs. Irvine H. Page, F.A.C.P., and Arthur C. Corcoran, in the Research Division of the Cleveland Clinic, on the determination of the action of active adrenal steroids in dogs and in patients with hypertension.

Stefan Stanislaus Fajans, M.D., Ann Arbor, Mich. A graduate of the University of Michigan (B.S., 1938; M.D., 1942), Dr. Fajans interned at the Mount Sinai Hospital, New York City, and served as medical officer in the U. S. Army. Returning to Ann Arbor in 1946, he has since held appointments in the University Hospital as research fellow, assistant resident, and resident, in internal medicine. Dr. Fajans' application was granted to enable him to undertake studies with Jerome W. Conn, M.D., F.A.C.P., in the Metabolism Research Unit and the Endocrinology and Metabolism Clinic of the University Hospital, to determine the physiological mechanisms capable of either stimulating or depressing the Islets of Langerhans.

Horace William Gerarde, M.S., M.D., of Rockford, Ill. Dr. Gerarde, an exchange interne at the University of Iowa Hospitals, Iowa City, received his B.S. and M.S. in Chemistry degrees from Beloit College, and completed his medical course at the University of Wisconsin Medical School in 1948. He has held teaching assistantships in both institutions. During 1949–1950 Dr. Gerarde will study the histochemistry of certain liver diseases, under the direction of Drs. Mattill and Womack of the Departments of Biochemistry and Surgery, The State University of Iowa.

John Coleman Laidlaw, M.A., M.D., of Toronto, Canada. A former medical officer of the Royal Canadian Navy, Dr. Laidlaw attended the University of Toronto, where he obtained the B.A. degree in 1941, the M.D. in 1944, and the M.A., in biochemistry, in 1947. He has served as interne in the Toronto General Hospital and as demonstrator in biochemistry in the University of Toronto. Now an assistant lecturer in biochemistry in the University College, London, England, Dr. Laidlaw pro-

poses to continue studies there under Professor F. G. Young on the metabolism of certain cholinesterase inhibitors in regard to myasthenia gravis. Dr. Laidlaw has been designated by the Board of Regents as the ALFRED STENGEL RESEARCH FELLOW for 1949–1950.

JAMES METCALFE, JR., M.D., of Pigeon Cove, Mass. Presently a Lieutenant in the U. S. Navy, assigned to the Naval Hospital at Newport, R. I., Dr. Metcalfe is a graduate of Brown University (1943), and of the Harvard Medical School (1946). Before entering the Navy, he served as a medical house officer in the Peter Bent Brigham Hospital, Boston, 1946–1947. Dr. Metcalfe will devote his fellowship year to an investigation of the dynamics of circulation, with Dr. Eugene M. Landis, F.A.C.P., in the Department of Physiology, Harvard Medical School.

SAMUEL MOORE PEACOCK, JR., M.D., Philadelphia, Pa. Dr. Peacock is a Bachelor of Arts, Princeton University, 1944, and Doctor of Medicine, University of Pennsylvania School of Medicine, 1948. He is now an interne in the Bryn Mawr Hospital, Bryn Mawr, Pa. As a medical student, Dr. Peacock served as research assistant in the Eldridge R. Johnson Foundation for Medical Physics and the Department of Physical Medicine of the University of Pennsylvania. His fellowship will enable him to return to those departments to conduct cytochemical studies of nervous tissues during growth and other physiological activity, under the direction of Drs. Robert Hodes and Steven M. Horvath.

JACK LEONARD STROMINGER, M.D., Flushing, N. Y. An interne at the Barnes Hospital, St. Louis, Dr. Strominger received his A.B. degree from Harvard University in 1944, and his M.D. from the Yale University School of Medicine in 1948. It is his plan to devote his fellowship to studies of the microchemistry of brain tissue, with Professor O. H. Lowry in the Department of Pharmacology of the Washington University School of Medicine.

EDGAR WOODY, JR., M.D., Nashville, Tenn. Dr. Woody graduated from the University of Georgia in 1941 and took his M.D. degree from the Johns Hopkins University School of Medicine in 1944. Following an interneship in the Union Memorial Hospital, Baltimore, Dr. Woody had military service from 1945 to 1947, and then was appointed to interneships in pathology and in medicine in the Vanderbilt University Hospital. He will continue studies, now under way in the Departments of Medicine and Pathology of Vanderbilt University School of Medicine, on the combined effect of potassium iodide and streptomycin in tuberculosis.

Change in Subscription Rate

ANNALS OF INTERNAL MEDICINE

The subscription rate of $7.00, domestic, and $8.00, foreign, for the ANNALS OF INTERNAL MEDICINE has remained unchanged from the inception of the Journal in 1926 to the end of 1948. The cost of producing this Journal has increased 118% since 1940 and the number of pages has been increased over 13% since 1943. The Board of Regents, at their meeting on November 7, 1948, voted to increase the rate of subscriptions from $7.00 to $10.00, domestic, and from $8.00 to $11.00, foreign, as of January 1, 1949. Members who pay dues will continue to receive the Journal as a part of their membership without further charge.

The increase in the subscription rate is moderate in comparison with the increased cost of publication. The great majority of medical journals have long since increased their subscription rates, in many instances by a much larger percentage than that now being put into effect by the College.

The American College of Physicians' Directory

The last complete Directory of the American College of Physicians, containing biographical data of all members, was published during 1941. Due to labor and paper shortages during and immediately after the War, Membership Rosters only have been published, the last edition being for 1948.

The Board of Regents has now authorized the complete revision and republication of the Directory during 1949. The cost will have increased over 1941 by nearly 300%. The prepublication price of the Directory to members of the College will be $4.00; the price to non-members, institutions and others, $5.00. In due course, Directory questionnaires, with prepublication order forms, will be distributed to all members of the College.

New Life Members

Grateful acknowledgment is made of recent subscriptions to Life Membership by the following Fellows of the American College of Physicians:

Walter M. Solomon, Cleveland, Ohio
John W. Wilce, Columbus, Ohio
J. C. Zillhardt, M.D., Binghamton, N. Y.

Charles S. Bluemel, M.D., F.A.C.P., Denver, Colo., has generously given to the College Library of Publications by Members a copy of his new book, "War, Politics, and Insanity," published by The World Press, Inc., 1817 California St., Denver 2, Colo., 1948.

Associates Should Attend A.C.P. Annual Session

Attendance at one or more Annual Sessions by Associates before proposal for advancement to Fellowship is prescribed by regulations of the Board of Regents of the American College of Physicians. This regulation was temporarily discontinued during World War II, from 1942 to 1946, because it became obviously impossible for Associates in the armed services to attend and because the Annual Sessions of the College had to be abandoned during part of that time. The regulation is now again in full effect. It is maintained that an Associate must display an abiding interest in the College and in internal medicine or its allied branches. There is no better way in which such an interest can be displayed than by attendance at the Annual Sessions of the College, accepted as the most important postgraduate week in the field on this Continent.

Proposal of Candidates

The By-Laws of the American College of Physicians require that proposals of candidates for election to Associateship or Fellowship be filed at least 60 days in advance of action by the Credentials Committee. The next meetings of the Committee are scheduled for February 26 and 27, 1949, and March 26, 1949.

Virginia Held A.C.P. Regional Meeting, at Richmond, October 19

The Virginia Regional Meeting of the American College of Physicians was held at the John Marshall Hotel, Richmond, on October 19, during the meeting of the Medical Society of Virginia. Dr. Staige Blackford, F.A.C.P., Charlottesville, presided as Chairman of the section.

Dr. Charles M. Caravati, F.A.C.P., Richmond, reported to the group on the proceedings of the Board of Governors and the Board of Regents at the San Francisco Annual Session, which he had attended as the alternate Governor for Virginia. Dr.

William B. Porter, F.A.C.P., a representative of the American College of Physicians on the American Board of Internal Medicine, spoke at some length concerning the problems of the Board, its examinations, etc. Dr. J. Morrison Hutcheson, F.A.C.P., Richmond, a former Regent and a former Officer of the College, discussed the qualifications, standards and obligations of members of the College in relation to their communities and in relation to maintaining the highest type of standards in the practice of internal medicine.

Dr. A. Brownley Hodges, F.A.C.P., Norfolk, was unanimously elected Chairman for the coming year, and Dr. James F. Waddill, F.A.C.P., was elected Secretary-Treasurer. The group voted to hold the scientific meeting of the Virginia section at Norfolk sometime early in 1949.

New Jersey Regional Meeting Newark, November 5, 1948

A large and enthusiastic gathering of members of the College and their guests attended the second annual A.C.P. regional meeting for New Jersey, held under the Governorship of George H. Lathrope, M.D., F.A.C.P., at the Academy of Medicine of Northern New Jersey and the Downtown Club, in Newark. Jerome G. Kaufman, M.D., F.A.C.P., Newark, was chairman of arrangements, and John E. Leach, M.D., F.A.C.P., Paterson, chairman of program. President Walter W. Palmer, New York, and Dr. Alex. M. Burgess, A.C.P. Regent and member of the American Board of Internal Medicine, were guest speakers after dinner. Lemuel C. McGee, M.D., F.A.C.P., Wilmington, Governor for Delaware, and Asa L. Lincoln, M.D., F.A.C.P., New York City, Governor for Eastern New York, presided over the afternoon scientific sessions.

The following scientific program was presented: Diagnosis and Treatment of Hepatic Cirrhosis, Andrew J. V. Klein, M.D., F.A.C.P., Newark, N. J. Ulcerative Colitis: When Should the Internist Advise Surgical Intervention? Manfred Kraemer, M.D., F.A.C.P., Newark, N. J. Insulin Sensitivity, Nathan Swern, M.D., F.A.C.P., Trenton, N. J. Electrocardiographic Booby-Traps, Levi M. Walker, M.D. (Associate), Atlantic City, N. J. Hodgkin's Disease, Its Relation to Other Neoplasms of Lymphoid Tissue, William G. Bernhard, M.D., F.A.C.P., Newark, N. J. The Rôle of Allergy in Internal Medicine, Robert A. Cooke, M.D., F.A.C.P., New York, N. Y.

Conference Committee on Graduate Training in Medicine

This Conference Committee on Graduate Training in Medicine has been fully reactivated and will participate with the Council on Medical Education and Hospitals in the inspection and approval of hospitals for graduate training, including residencies. The Committee consists of two representatives each from the American College of Physicians, the American Board of Internal Medicine and the Council on Medical Education and Hospitals. Those representatives are as follows:

For the American College of Physicians:
Dr. LeRoy H. Sloan, F.A.C.P., Chicago, Ill.
Dr. Reginald Fitz, F.A.C.P., Boston, Mass.
For the American Board of Internal Medicine:
Dr. Roy W. Scott, F.A.C.P., Cleveland, Ohio
Dr. Walter L. Palmer, F.A.C.P., Chicago, Ill.
For the Council on Medical Education and Hospitals:
Dr. William S. Middleton, F.A.C.P., Madison, Wis.
Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio

Extensive plans are being rapidly consummated for the initiation of a fully adequate plan of inspection of hospitals.

The National Foundation for Infantile Paralysis Announces Postgraduate Fellowships

Research

Research fellowships are available in virology, orthopedic surgery, pediatrics, epidemiology, and neurology. These fellowships are intended to emphasize (1) advanced training in the basic sciences as they apply to the particular specialty and to research, and (2) experience in research, which need not be immediately related to poliomyelitis.

Eligibility requirements: Doctor of Medicine (or when appropriate, a degree of Doctor of Philosophy); a minimum of two years of training on the residency level in the specialized field; presentation of an appropriate program of study and investigation; United States citizenship; sound health, as attested by a physical examination.

Physical Medicine

Clinical fellowships are available to physicians who wish to prepare for eligibility for certification by the American Board of Physical Medicine.

Eligibility requirements: Graduation from a Class A school of medicine; completion of a rotating internship of not less than one year in a hospital approved by the Council on Medical Education and Hospitals of the American Medical Association; license to practice medicine in one or more states; citizenship in the United States; sound health, as attested by a physical examination; age limit: 40.

Public Health

Fellowships are available to physicians for one year of postgraduate study leading to a Master of Public Health degree at a school of public health approved by the American Public Health Association.

Eligibility requirements: Graduation from a Class A school of medicine; completion of an internship of not less than one year in a hospital approved by the Council on Medical Education and Hospitals of the American Medical Association; license to practice medicine in one or more states; citizenship in the United States; sound health, as attested by a physical examination.

Application may be made to the National Foundation for Infantile Paralysis, 120 Broadway, New York 5, New York, at any time during the year. Selection of candidates will be made on a competitive basis by committees composed of specialists in each field. Awards are based on the individual need of each applicant.

University of California Medical School's Program of Postgraduate Instruction, 1949

The following courses are offered: Psychiatry for General Practitioners (January 31 through February 4); Cardiology (January 31 through February 4); Gastroenterology (February 7 through 11); Endocrinology, Including Diabetes (June 20 through 24); Symposium on Tumors (June 27 through 29); Obstetrics and Gynecology (July 5 through 8); Otorhinolaryngology (September 5 through 9); Ophthalmology (September 12 through 16); Continuation Course in General Medicine (September 19 through December 5); Diseases of the Chest (December 5 through 9).

For detailed information write: Dr. Stacy R. Mettier, Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22, California.

Research Grants and Fellowships to Be Made Available in 1949 by the Life Insurance Medical Research Fund

Applications for grants in aid of research on cardiovascular problems to begin in 1949 will be received by the Life Insurance Medical Research Fund up to January 15, 1949. Support is available for physiological, biochemical, and pathological research which bears on cardiovascular problems, as well as for clinical investigation in this field. Preference is given to fundamental research. It is expected that about $500,000 will be awarded for these grants.

Applications for postgraduate fellowships for training in research in 1949–50 will be received by this Fund up to January 1, 1949. Preference is given to candidates who wish to work in the broad field of cardiovascular function or disease and to candidates who wish to work in institutions other than those in which they have obtained most of their experience. A doctor's degree (M.D. or Ph.D.) or the equivalent is required. The annual stipend varies as a rule being between $2,500 and $3,500, with larger amounts in special cases. Approximately 12 fellowships will be available.

Later in the year, the Fund will also offer a number of student (pre-doctoral) research fellowships for 1949–50.

Both grants and fellowships will become available on July 1, 1949.

Further information and application blanks may be secured from the Scientific Director, Life Insurance Medical Research Fund, 2 East 103d Street, New York 29, New York.

Course in Electrocardiographic Interpretation

A course in Electrocardiographic Interpretation for *graduate physicians* will be given at the Michael Reese Hospital Postgraduate School under the personal direction of Dr. Louis N. Katz, Director of Cardiovascular Research. The class will meet each Wednesday from 7:00 p.m. to 9:00 p.m. for a period of 12 weeks, beginning February 9, 1949.

Further information and a copy of the lecture schedule may be obtained on application to Dr. Samuel Soskin, Dean, Michael Reese Hospital Postgraduate School, 29th Street and Ellis Avenue, Chicago 16, Illinois.

30TH ANNUAL SESSION

THE AMERICAN COLLEGE OF PHYSICIANS

WALDORF-ASTORIA HOTEL

NEW YORK, N. Y.

March 28–April 1, 1949

The program of General Sessions and Morning Lectures is in charge of the President, Dr. Walter W. Palmer, Public Health Research Institute, Foot of East 15th Street, New York, 9, N. Y. All places are at this time filled, and the program will be published in the February, 1949, Issue of this journal. Many new names and new topics of timely interest have been chosen. The Convocation for the induction of new Fellows and Masters, and the presentation of the John Phillips Memorial Award, the James D. Bruce Memorial Award and the Alfred Stengel Memorial Award, and the announcement of the Research Fellowships, will be held on Wednesday evening, March 30. A distinguished man of national repute will deliver the convocational Lecture.

The program of Hospital Clinics, Panel Discussions, Clinico-Pathological Conferences and entertainment (except for ladies' entertainment) is in charge of the General Chairman, Dr. Franklin M. Hanger, 620 W. 168th Street, New York 32, N. Y. Hospital Clinics will be held on Tuesday and Thursday mornings; many will be conducted in reasonably near-by hospitals and some will be conducted at the Waldorf-Astoria Hotel, some of the distant hospitals, such as in Brooklyn and the Veterans Administration, having arranged to present their clinics at the hotel, and thus save attendants from traveling longer distances. Even the clinics conducted at the hotel will be of highly practical nature with the showing of patients. Panel Discussions covering a wide field of timely topics will be held daily at the hotel, Tuesday through Friday, from 12:00 m. to 1:15 p.m. The Annual Banquet will be held in the Grand Ballroom of the Waldorf-Astoria Hotel on Thursday evening, March 31. An eminently qualified speaker has been engaged. A highly appropriate program of entertainment is being arranged for all, with many unique features for the ladies under the Chairmanship of Mrs. Edgar Stillman. Time is being set aside for theater parties, visits to Radio City, the United Nations, etc.

Hotel Accommodations. The Waldorf-Astoria Hotel, Park Avenue and 50th Street, will be official headquarters where registration and meetings will be held. The Belmont-Plaza Hotel, Lexington Avenue and 49th Street, will be supplementary headquarters for housing of speakers and participants in the program. Officers, Regents, Governors and Committeemen of the College and Speakers on the Program should apply for accommodations directly to Mr. E. R. Loveland, Executive Secretary of the College, and not to the Housing Bureau or to hotels direct. Hotel Lexington, Lexington Avenue and 48 Street, has been assigned to the Exhibitors, who should make application for their hotel accommodations through the Medical Exhibitors Association, 616 Stock Exchange Building, Philadelphia 2, Pa.

A fully adequate number of first-class guest rooms has been reserved at near-by hotels within a ten-minute walk of the Waldorf-Astoria Hotel. The Housing Bureau, working through the Committee on Hotels and Transportation, has been set up at 500 Park Avenue, New York 22, N. Y. Applications for rooms should be made to this Bureau, which will make every effort to assign accommodations in keeping with the applicant's wishes. It is necessary that five choices of hotels be indicated, and that a reasonable range of rates desired be shown. Whenever possible, arrangements should be made for occupancy of rooms accommodating two persons. Hotels will

confirm each reservation after its receipt from the Housing Bureau. All applicants are urgently requested to notify the Housing Bureau promptly if they find it impossible to attend, thus releasing their accommodations to other physicians.

List of Hotels

Hotel	*Type of Room and Rate* *
Waldorf-Astoria Park Avenue and 50th Street	100 doubles—$10.00 to $16.00 25 suites—18.00 to 32.00
Belmont-Plaza Lexington Avenue and 49th Street	90 doubles—$6.50 to $9.50 5 suites—12.00 to 15.00
Abbey 149 W. 51st Street	12 singles—$3.75 to $5.00 38 doubles—6.00 to 8.00
Ambassador Park Avenue and 51st Street	10 doubles—$9.00 to $14.00 5 suites—16.00 to 25.00
Barclay 111 E. 48th Street	50 doubles—$11.00 to $13.00
Biltmore Madison Avenue and 43d Street	100 doubles—$10.00 to $17.00
Commodore Lexington Avenue and 42nd Street	70 singles or doubles: singles—$5.50 to $7.50 doubles—8.50 to 10.00 200 twins—11.50 15 combinations—$13.00
Delmonico 502 Park Avenue	6 singles—$10.00 10 suites—18.00 to 22.00
Gotham Fifth Avenue and 55th Street	10 doubles—$9.00 to $14.00
New Weston 34 E. 50th Street	30 doubles—$8.00 to $10.00 5 suites—12.00 to 20.00
Park Central Seventh Avenue and 56th Street	50 doubles—$8.50 to $10.00 75 suites—10.00 to 14.00
Piccadilly 227 W. 45th Street	75 doubles—$6.00 to $8.00
Plaza Fifth Avenue and 59th Street	10 singles—$9.00 to $12.00 40 doubles—10.00 to 18.00
Roosevelt Madison Avenue and 45th Street	50 singles—$6.50 to $10.00 350 doubles—10.50 to 15.00
St. Regis Fifth Avenue and 55th St.	3 singles—$8.00 to $10.00 6 doubles—12.00 to 14.75
Shelton Lexington Avenue and 49th Street	25 singles—$4.50 to $6.50 75 doubles—6.50 to 8.00

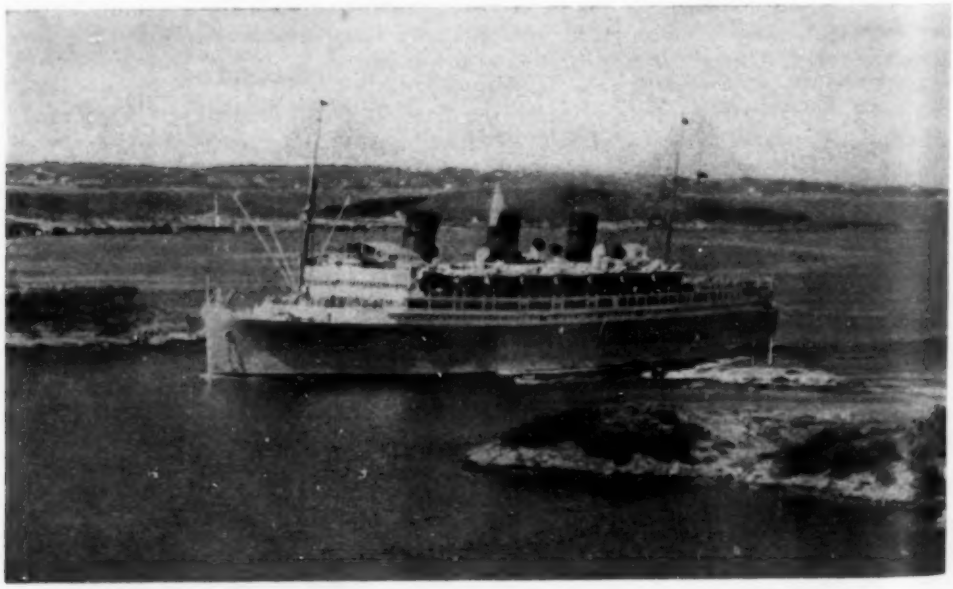
* Subject to 5% New York City Sales Tax.

Sheraton 303 Lexington Avenue	10 doubles—$8.00 to $10.00 10 suites—10.00 to 12.50
Taft Seventh Avenue and 50th Street	50 singles—$4.00 to $7.00 150 doubles—6.50 to 9.00
Vanderbilt (10 minutes by cab) Park Avenue and 34th Street	10 singles—$4.50 to $7.00 15 doubles—8.00 to 10.00
Victoria Seventh Avenue and 51st Street	10 singles—$5.00 65 doubles—7.00 to 9.00
Warwick 65 W. 54th Street	75 doubles—$12.00 25 suites—20.00
Wentworth 59 W. 46th Street	20 doubles—$7.00 to $8.00 15 suites—12.00 to 14.00
Winthrop Lexington Avenue and 47th Street	6 doubles—$7.00 to $9.00

* Subject to 5% New York City Sales Tax.

POST-CONVENTION CRUISE

Following 30th Annual Session A.C.P., New York City



The *Queen of Bermuda* at Two Rock Channel en route to Hamilton Harbor.

The Convention Tour to and from the San Francisco Annual Session of the College during the spring of 1948 met with such acclaim among those who took ad-

vantage of it that numerous requests have come in for some other post-convention event in 1949, which led to the decision to conduct a Post-Convention Cruise to Bermuda following the 30th Annual Session in New York City from March 28 through April 1, 1949. The cruise has been arranged to leave New York City at 12 o'clock noon, Monday, April 4, using the steamship, *Queen of Bermuda,* with the following schedule:

April 4—Leave New York 12:00 noon; Upper and Lower Bays, the famous skyline, tea, dancing.

April 5—The Gulf Stream, a lazy day at sea. Movies, Tea, Concert, Dancing.

April 6—Bermuda. Arrive Five Fathom Hole at 7:00 a.m. and cruise along the colorful North Shore into Great Sound and Hamilton Harbor, one of the loveliest in the world. Go ashore at 9:00 a.m. Hotel Bermudiana.

April 7—Motor or carriage drives to St. George's, Somerset, Gibb's Hill, or Spanish Point; time to visit the celebrated caves and coral underseas gardens; to shop; to golf; to follow the camera or other diversions.

April 8—Leave Hamilton, 3:00 p.m. via the Great Sound and North Shore.

April 9—Again in the Gulf Stream; a variety of entertainment.

April 10—Monday; arrive New York, 9:00 a.m.

Bermuda is a delightful vacation center with landscapes and marine views enchanting in their loveliness.

A quiet cove in Hamilton Harbor.

The *Queen of Bermuda* is one of the handsomest and most luxuriously equipped ships coming into New York.

A special, illustrated booklet is being prepared. For full information, plan of the ship, booklet on Bermuda, and answers to your questions, write to Mr. Leon V. Arnold,

Travel Consultant, 36 Washington Square West, New York, 11, N. Y. Mr. Arnold handled the Bermuda arrangements for the American College of Physicians in 1938 and will be the official conductor in 1949.

A.C.P. Postgraduate Courses

Spring, 1949, Schedule

The following schedule of courses has been approved by the Advisory Committee on Postgraduate Courses and the Board of Regents for the spring of 1949. The Preliminary Postgraduate Bulletin will be published during December and distributed to all members of the College and to those who have requested the entry of their names on the non-member mailing list. A registration form will accompany the Postgraduate Bulletin.

Medical Aspects of Nuclear Energy—Bureau of Medicine and Surgery, U. S. Navy, Medical Department of the U. S. Army, the Armed Forces Special Weapons Project, the Atomic Energy Commission, the Air Force, the U. S. Public Health Service, and the Veterans Administration, Washington, D. C.; Lt. Col. Karl Houghton, (MC), USA, Chairman; eight days, January 24–February 1, 1949; Fee: $40.00, A.C.P. Members; $80.00, Non-members; free to medical officers from the participating agencies.

The class will meet at the Sternberg Auditorium, Army Medical Center, Washington, D. C., where excellent facilities are available, such as the new radiation laboratory for demonstrations and instrument problems. One of the big problems in this field is the education of both service and civilian physicians. Never before have all agencies combined to make available, through the American College of Physicians, a course of such importance and significance. The medical profession has a moral responsibility to learn all that is available on this subject. An effort will be made to include the nature of ionizing radiation as it relates to atomic fission, the methods of detection and evaluation of the hazard, the biological effects of radiation, the possibilities of protection and avoidance, and present concepts of treatment. Two days may be added to the course to cover the Medical Effects of Atomic Explosion. Specific information on isotopes and laboratory procedures has been added to the course.

Registration for this course is immediately available on application for registration forms.

Gastro-Enterology—University of California Medical School and Stanford University School of Medicine, San Francisco, Calif.; T. L. Althausen, M.D., F.A.C.P., and Dwight L. Wilbur, M.D., F.A.C.P., Directors; one week, February 7–12, 1949; Fee: $30.00, A.C.P. Members; $60.00, Non-members.

The detailed outline of this course has been published and is available. Registration should be consummated without delay. It is anticipated there will be facilities for several non-members.

The Hematologic Emphasis in Clinical Medicine—Ohio State University College of Medicine, Columbus, Ohio; Charles A. Doan, M.D., F.A.C.P., Director; one week, February 14–19, 1949; Fee: $30.00, A.C.P. Members; $60.00, Non-members.

This is a repetition of a course that has been most successfully given on previous occasions. It is one of exceptional merit.

Internal Medicine—Massachusetts General Hospital, Boston, Mass.; James H. Means, M.D., F.A.C.P., Director; two weeks, March 7–19, 1949; Fee: $60.00, A.C.P. Members; $120.00, Non-members.

It has been several years since Dr. Means directed a course for the College, and special gratification is felt by the members for the opportunity to take this exceedingly fine course again.

ELECTROCARDIOGRAPHY—Massachusetts General Hospital, Boston, Mass.; Conger Williams, M.D., Director; one week, April 25–30, 1949; Fee $60.00, A.C.P. Members; $120.00, Non-members.

This course was first given during May, 1948. The class was oversubscribed, and early registration is recommended to members of the College. It would appear improbable that many non-members can be accommodated. The course is designed to acquaint the student with the modern theory of electrocardiography and its clinical application.

CARDIOLOGY—Philadelphia Institutions; William G. Leaman, Jr., M.D., F.A.C.P., Director; one week, May 2–7, 1949; Fee: $30.00, A.C.P. Members; $60.00, Non-members.

The class will meet at the Philadelphia General Hospital. The faculty for this course will include leading teachers in cardiology from various medical schools of Philadelphia and other institutions of the East. Early registration is recommended because it is anticipated that the demand may exceed the facilities.

PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE—University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; Julius H. Comroe, Jr., M.D., F.A.C.P., Director; one week, May 9–14, 1949; Fee: $30.00, A.C.P. Members; $60.00, Non-members.

This course was first given during 1947 by Dr. Comroe and was one of the most popular courses ever organized under the College. It is planned for internists who are interested in learning why symptoms occur, how drugs act, and why and how clinical physiological tests are used in diagnosis. The faculty will consist of many authorities from Philadelphia institutions and also from other cities, such as Boston, New York, Baltimore, Chicago, Cleveland, and elsewhere.

ALLERGY—University of Pittsburgh School of Medicine, Pittsburgh, Pa.; Leo H. Criep, M.D., Director; one week—May 16–21, 1949; Fee: $30.00, A.C.P. Members; $60.00, Non-members.

At the time this announcement is sent to press, this course is yet in a tentative state. The course, however, has been approved by the College and awaits assignment of a date and other details. A close, coöperative plan with the University of Pittsburgh, the American Academy of Allergy, and the American College of Physicians will be established, and the course should be extremely valuable to the internist who wishes instruction in allergy, as well as to the allergist who desires to be kept up-to-date.

ENDOCRINOLOGY—Tufts College Medical School, Boston, Mass.; Edwin B. Astwood, M.D., F.A.C.P., Director; one week, June 13–18, 1949; Fee: $30.00, A.C.P. Members; $60.00, Non-members.

This is a new course on the College schedule. All of the details have been concluded, and it is confidently expected that this course will be one of the outstanding courses on the College program.

Preliminary Outline A.C.P. Postgraduate Course
Medical Aspects of Nuclear Energy
Washington, D. C., Jan. 24–Feb. 1, 1949

	Mon., Jan. 24	Tues., Jan. 25	Wed., Jan. 26	Thurs., Jan. 27	Fri., Jan. 28	Mon., Jan. 31	Tues., Feb. 1
A.M. 9:00 – 10:00	Introduction and Scope of Course	Informal Discussion of Basic Physics	Radiation Detection and Measurement	Physical and Laboratory Diagnosis of Radiation Injury	Production of Radioisotopes	Laboratory Instrumentation	Uses of I^{131}
10:00 – 11:00	Basic Atomic and Nuclear Physics	Types of Personnel Injuries at Hiroshima and Nagasaki		Therapy of Radiation Injury	Procurement and Safe Handling of Radioactive Material	Assay of Radioactive Material	Uses of P^{32}
11:00 – 12:00		Biological Effects of Ionizing Radiation	Fundamentals of Radiation Pathology	Therapy and Handling of Mechanical and Thermal Injuries	Decontamination Problems	Dosage Calculation	Uses of Na^{24}
P.M. 1:00 – 2:00	Radioactivity and Properties of Particles			Internal Radiation Hazard	Diagnostic and Therapeutic Use of Isotopes	Principles of Tracer Techniques	Uses of Miscellaneous Isotopes
2:00 – 3:00	Fission and Bomb Phenomena	Radiation Sickness	Radiological Defense Problems	Psychological Implications of Atomic Bombing	International Implications of Nuclear Energy	Principles of Radiochemistry	Isotope Laboratory Organization and Administrative Problems
3:00 – 4:00	Nuclear Energy —British Film Parts I, II, III	Nuclear Energy —British Film Parts IV, V	Medical Effects of Atomic Bombs Japanese Film	Nuclear Energy March of Time Film and Operations Crossroads		Radioautographic Techniques	Guest Speaker

OBITUARIES

Dr. James Alexander Miller, President of the American College of Physicians in 1935–1936, died at his summer home in Black Point, Conn., July 29, 1948.

DR. JAMES ALEXANDER MILLER

Dr. Miller was born in Roselle, N. J., March 24, 1874. He was graduated from Princeton University in 1893 and received his A.M. degree there in 1894. His medical degree was awarded by the College of Physicians and Surgeons, Columbia University, in 1899. Early in his medical career, he spent his summers in association with Dr. Edward Livingston Trudeau at Saranac Lake. Dr. Miller was greatly inspired by this personal and professional association, and its influence lasted throughout his life. Seeing the need of organized social, public health, and medical work against tuberculosis, Dr. Miller soon became identified with organizations in New York City through which he was able to direct his efforts. These included the Charity Organization Society, the New York Tuberculosis and Health Association, and the Tuberculosis Service of Bellevue Hospital. He came in close contact with the numerous aspects of the tuberculosis problem and was early convinced of the necessity of directing the attack from various fronts. In the public health field he helped organize the New York Tuberculosis and Health Association and the National Tuberculosis Association, serving as President of the former from 1920 to 1929, and of the latter in 1921 and 1922. In the social service field he continued active in the Community Service Society which was partly the offspring of the Charity Organization Society. At Bellevue Hospital he interested a group of loyal associates who helped him transform an unspeakably neglected tuberculosis service into one of the most outstanding of its type in the world. At the same time, recognizing the great need for medical education in this branch of medicine, Dr. Miller organized a course of instruction for his resident hospital staff and also for the students of the College of Physicians and Surgeons of Columbia University. In these relationships he served as Visiting Physician in Charge of the Tuberculosis Service, and Professor of Clinical Medicine. Simultaneously, he assumed more and more responsibility for the development of the work at Trudeau Sanatorium, finally serving as President of the Board of Trustees for a number of years.

These activities indicate only in small degree the scope of his interest and resourcefulness, the ample reserve of energy with which he was endowed, and the limitless generosity with which he gave of his time and talents to many worthy projects. He was President of the American Climatological and Clinical Association in 1914 and a member of various other medical societies. From 1945 until the time of his death, he was an alumni trustee of Columbia University.

In the American College of Physicians Dr. Miller's record of contributions is most distinguished, and was recognized by the award of Mastership in 1941. He served as a member or chairman of numerous committees, including the Board of Regents,

the Executive Committee, the Committee on Standards of Admission, the Committee on Public Relations and the Committee on Future Policy for the Development of Internal Medicine. His leadership as President was outstanding, and his energy and farsightedness lent a great impetus to the sound and progressive development of the College. He did much to define its objectives, including educational activities, sound finance, the establishment of a permanent home in Philadelphia and the creation of the American Board of Internal Medicine. He exercised similar leadership in other organizations and became the President of the New York Academy of Medicine from 1937 to 1938. In 1947 the Academy awarded him a medal in recognition of his unique position as "its most distinguished and beloved Fellow and one of the great benefactors of mankind." Numerous other honors came to him, including the Trudeau Medal of the National Tuberculosis Association in 1944, election as a Chevalier of the French Legion of Honor in 1918, following his service in the American Red Cross and as Medical Director of the Rockefeller Commission for the Prevention of Tuberculosis, and honorary degrees from Princeton (Sc.D., 1936), Columbia (Sc.D., 1930) and New York Universities (Dr. P. H., 1937).

The logical succession of Dr. Miller to leadership in so many activities is explained by his administrative capacity, his vision, his ability to penetrate problems, evaluate their merits and formulate practical solutions, and his appreciation of the qualities of men and his ability to inspire them to exercise these qualities for useful purposes. He recognized no limit of progress or improvement in the organizations and projects in which he was interested and could always see a better future, but was sufficiently realistic to know that progress could be achieved only by gradual steps and hard work. He never spared himself in sharing the labor; thus, through his magnanimity, fine spirit and constant hope, he stimulated many others to work with him toward the ideal. With all this, he cared for a busy private practice and became the leader in tuberculosis work in his community. He had an ample following of loyal and admiring patients. There are few physicians who have ever won the gratitude of a community like that which came to Dr. Miller, and few who have exemplified the best qualities of a physician in so many ways.

J. Burns Amberson, M.D., F.A.C.P.

DR. JEREMIAH FLETCHER LUTZ

Jeremiah Fletcher Lutz, M.D., F.A.C.P., of Glen Rock and York, Pa., died in the Veterans Administration Hospital, Fort Howard, Md., of generalized atherosclerosis on September 11, 1948, and was buried in Glen Rock with Masonic rites. Dr. Lutz had retired from active practice about four months previously because of failing health.

Born in Baltimore on November 25, 1872, Dr. Lutz attended the Baltimore Polytechnic Institute, Sadler's Bryant and Stratton Business College, and received his medical degree in 1894 from the College of Physicians and Surgeons of Baltimore, now amalgamated with the University of Maryland School of Medicine. He interned at the Bay View Hospital (now the Baltimore City Hospital, 1894–96, and pursued postgraduate work at the New York Polyclinic Hospital, Presbyterian Eye, Ear, Nose and Throat Hospital, the Baltimore School of Roentgenology, and the Johns Hopkins University School of Medicine (under Dr. F. H. Baetjer). He took numerous other shorter courses in radiology. Licensed to practice in Maryland and Pennsylvania, Dr. Lutz limited his work to radiology in 1917, and subsequently became a diplomate of the American Board of Radiology.

During World War I, Dr. Lutz served as chief of the X-ray Department in the Army General Hospital No. 2, at Fort McHenry, Md., with rank of Major. He was roentgenologist, 1920–26, to the Kernan Hospital for Crippled Children, Baltimore; also, 1921–24, to the Sinai Hospital, and, 1921–26, to the Baltimore Eye and Ear

Hospital. He served the York Hospital, York, Pa., in a similar capacity from 1930 until his retirement in 1948. During the recent War, Dr. Lutz was associate roentgenologist to Medical Advisory Board No. 4, and examining physician to Local Board No. 1, Pennsylvania Selective Service. He was a member of the Pennsylvania State Medical Society, Philadelphia Roentgen Ray Society, and the Society for the Study of Neoplastic Diseases; a past president of the York County Medical Society and the York County Medical Club; a Fellow of the American Medical Association, the Radiological Society of North America, the American College of Radiology, and, since 1939, the American College of Physicians. Prominent in Masonic circles, Dr. Lutz was affiliated with numerous organizations and delivered many illustrated lectures on the "History of Masonry," the product of years of painstaking research. He was also the author of a number of published papers on radiology.

To a rare degree, Dr. Lutz combined thorough generalized clinical and specialized training, fine judgment and genuine human sympathy. Over a long period of years, he had given unselfishly of his services to every phase of organized medicine, and he will be deeply mourned by a large host of friends, both in and out of the profession, as well as by the members of his most devoted family.

JULIUS H. COMROE, SR., M.D., F.A.C.P.

MR. WILL C. BRAUN

Probably never before have these columns contained the obituary of a layman. Mr. Will C. Braun, Business Manager Emeritus of the American Medical Association, stands in a category all his own. He was born August 24, 1868, and died September 12, 1948, at the age of 80 years. He had devoted 56 of those 80 years to the work of the American Medical Association and was the most widely known layman associated with the medical profession. He had a large hand in the history and growth of his organization, dating back to its early beginnings and carrying through to the great organization it is today. He served actively until 1946 as the Business Manager and then was retired, being succeeded by Mr. Thomas R. Gardiner.

Mr. Braun will be affectionately remembered by a great host of physicians, by advertisers, exhibitors, and the numerous organizations that had frequent contact with him over so many years.

E. R. LOVELAND

DR. EDWARD WINFIELD MISKALL

Dr. Edward Winfield Miskall died suddenly of coronary occlusion, on his forty-eighth birthday on August 13, 1948, in the midst of an active cardiologic practice in East Liverpool, Ohio. He was born and reared in East Liverpool, and received his Bachelor of Science degree in 1924, and his medical degree in 1926 from the Ohio State University. He served his internship at Mercy Hospital, Springfield, Mass. Following a period of general practice, he went to the Massachusetts General Hospital, where, for two years, he indulged his interest and perfected his training in the special field of his choice under Dr. Paul White. Returning to East Liverpool in June 1934, he became an outstanding consultant in Cardiology, attracting patients from many communities in the Tri-State District. He was elected to fellowship in the American College of Physicians in 1936, and became a diplomate of the American Board of Internal Medicine in 1945. He was a member of the medical staff and director of the Clinical Laboratories of the East Liverpool City Hospital. He served as City Health Commissioner for five years until the increasing demands upon his direct professional services prevented his continuing this activity. He was consulting cardio-

logist to the Salem City Hospital and was past president of the Columbiana County Medical Society.

Dr. Miskall continued throughout his relatively brief medical career to be a student of disease and made each patient the object of special and thorough study. The passing of Dr. Miskall has left a great void in his community. Both fellow physicians and patients had the highest respect for his professional ability.

CHARLES A. DOAN, M.D., F.A.C.P.,
Governor for Ohio

DR. ANDREW BAPTISTE RIVERS

Dr. Andrew B. Rivers was born December 10, 1894, at Rollingstone, Minn. He attended St. Francis College, St. Francis, Wis., from 1906 to 1913; received the degree of M.D. in 1917 from Creighton University and was an intern at the City and County Hospital, St. Paul, Minn., from July, 1917, to October, 1918. He served as lieutenant in the Medical Corps of the United States Navy during World War I. He was assistant in medicine at the University of Minnesota from May to November, 1919, and entered the Mayo Foundation as a fellow in medicine on January 15, 1920; received the degree of M.S. in Medicine in 1929 from the University of Minnesota and of M.A. in 1930 from St. Francis College. At the time of his death he was consultant in medicine, the Mayo Clinic, and associate professor of medicine, the Mayo Foundation, Graduate School, University of Minnesota.

Dr. Rivers was a fellow of the American College of Physicians and the American Medical Association, and a member of the American Gastro-Enterological Association, the Central Clinical Research Club, the Central Society for Clinical Research, Sigma Xi and Phi Beta Pi.

Dr. Rivers had published about ninety articles, chiefly in the field of gastroenterology, and at the time of his death was preparing a monograph on peptic ulcer. Dr. Rivers was a skilled internist with a great capacity for friendship. He was admired and respected by patients, students and associates. He died from acute coronary thrombosis on October 3, 1948.

E. V. ALLEN, M.D., F.A.C.P.,
Governor for Minnesota

DR. C. FREDERIC ROCHE

The name of Dr. C. Frederic Roche, beloved pioneer physician of Miami Beach Fla., is written indelibly into the record of growth of his chosen community. He established his practice there when Miami Beach was a struggling young resort, and at his death he was one of the outstanding physicians in the practice of internal medicine in the Miami area. Much of his time, effort and enthusiasm had been spent in the building of what is now a thriving city.

Dr. Roche was born in Bay City, Mich., in 1888. He was graduated in medicine from the University of Michigan in 1919 and began his practice in Florida shortly thereafter. He organized the Miami Beach Department of Health and served as its director for many years. He served as chief of the Cardiac Clinic and medical service of St. Francis Hospital and as staff member of Victoria Hospital, and was a past president of the Miami Heart Association. He became a Fellow of the American College of Physicians in 1930.

Throughout his career he was esteemed for his progressive attitude, his diligent efforts to better the health resources of his community, his kindness and devotion to his friends. He gave unsparingly and unselfishly of his strength and died at the peak of his career on January 17, 1948.

WILLIAM C. BLAKE, M.D., F.A.C.P.,
Governor for Florida

DR. THOMAS TROVILLO SHEPPARD

Thomas Trovillo Sheppard, M.D., of Pittsburgh, died July 5, 1948, at the age of 56.

A graduate of Yale University and, in medicine, of the Columbia University College of Physicians and Surgeons, Dr. Sheppard was for many years on the medical staff of the St. Francis, Western Pennsylvania, and Elizabeth Steele Magee Hospitals. He was assistant professor of medicine in the University of Pittsburgh and director of the Renziehausen Foundation for Diabetic Children in the Children's Hospital. A Fellow of the American Medical Association, Dr. Sheppard was a member of the Pittsburgh Academy of Medicine, Clinical Pathological Society of Pittsburgh, Pittsburgh Society for Biological Research, Allegheny County and Pennsylvania State Medical Societies and the American Diabetes Association. He became an associate of the American College of Physicians in 1928.

DR. FRANCIS H. SMITH

Dr. Francis Henney Smith, an outstanding Southern psychiatrist and a Fellow of the American College of Physicians since 1923, died at his home at Abingdon, Va., on July 1, 1948.

Born at Lexington, Va., April 12, 1881, Dr. Smith obtained the A.B. degree from Fredericksburg College and the M.D. degree from the Medical College of Virginia in 1904. He practiced for a time in Lewisburg, W. Va., before going to Abingdon where he served as an internist in the George Ben Johnston Memorial Hospital. Dr. Smith was a former president of the Medical Society of Virginia and a member of the Medical Examining Board of Virginia, as well as the Southwestern Virginia Medical Society, the Southern Medical Association, and the American Medical Association.

DR. CLARENCE M. TRIPPE

Dr. Clarence Morton Trippe of Asbury Park, a former president of the Charlotte, N. C., and Asbury Park, N. J., Medical Associations, and former vice president of the New Jersey Medical Society, died on August 25, 1948. He held the degrees of Bachelor and Master of Arts from Hamilton College and was a graduate of North Carolina Medical College and the College of Physicians and Surgeons of Columbia University. Following postgraduate studies in neuropsychiatry at the Neurological Institute and the Presbyterian and Roosevelt Hospitals in New York, Dr. Trippe served as Chief of Neurology in the Presbyterian, Mercy, and St. Peter's Hospitals, Charlotte, 1912–1915. During World War I he taught at Columbia University, and subsequently became Attending Neuropsychiatrist in the Veterans Administration Hospital, Lyons, N. J., and a member of the staff of Monmouth Memorial Hospital, Long Branch, N. J. A diplomate of the American Board of Neurology and Psychiatry, Dr. Trippe was a fellow of the American Medical Association and of the American College of Physicians, and a member of the Monmouth County Medical Society.

DR. CLARENCE KRAUS WEIL

Dr. Clarence Kraus Weil, an Associate of the American College of Physicians, died suddenly from coronary thrombosis in Montgomery, Ala., on May 5, 1948, at the age of 48 years. He was a native of Montgomery where he had continued to reside throughout his life. He received his B.S. degree from the University of Alabama in 1919, his M.D. degree from the Columbia University College of Physicians

and Surgeons in 1923, and did postgraduate work at Mount Sinai Hospital, New York. He was a veteran of World War II, having retired from the Army in 1946 with the rank of Lieutenant Colonel.

At the time of his death Dr. Weil was in active practice in Montgomery, where he was known for his interest in both civic and medical affairs. He had served as chairman of the Board of Censors and as president of the Montgomery County Medical Society; as counsellor for the Alabama State Medical Association; as vice chairman of the Section on Allergy of the Southern Medical Association. He was a diplomate of the American Board of Internal Medicine, a member of the Southeastern Allergy Association and the Chattahootchee Valley Medical Association, and a Fellow of the American Medical Association and the American Academy of Allergy.

Dr. Weil's death at the peak of his influence is regrettable.

E. Dice Lineberry, M.D., F.A.C.P.,
Governor for Alabama

DR. ANDREW BLAIR

Andrew Blair, M.D., F.A.C.P., a diplomate of the American Board of Internal Medicine, of Charlotte, N. C., died June 3, 1948. He was born at Carlisle, Pa., in 1896. He received his B.S. and A.M. degrees in 1921 and 1925, respectively, from Dickinson College. After graduating from the University of Pennsylvania School of Medicine in 1924, Dr. Blair thereafter served on the medical staffs of Presbyterian, Mercy, St. Peters, and Charlotte Memorial Hospitals in Charlotte, N. C. Dr. Blair was a member of the Medical Society of the State of North Carolina, and the Tri-State Medical Association; a former secretary of the Mecklenburg County Medical Society; a fellow of the American Medical Association and, since 1940, of the American College of Physicians.

DR. DANIEL DELOS COMSTOCK

Dr. Daniel Comstock was born in Tioga County, Pa., on April 29, 1880, and died in Oakland, Md., July 29, 1948, while vacationing there and recuperating from a previous heart attack. He received his preliminary education in Tioga County and attended business college in Elmira, N. Y. Later he joined staff workers at Battle Creek Sanitarium where he obtained nursing instruction. In 1902 he entered the American Medical Missionary College, from which he received his Doctor of Medicine degree in 1906. One year after graduating from medical school he came to California where he became prominent both in medical practice and education. In 1918 he became senior assisting physician, Los Angeles County Hospital, and in 1920, chief of the medical staff of the White Memorial Hospital and clinical professor of medicine in the College of Medical Evangelists.

Dr. Comstock was a diplomate of the American Board of Internal Medicine. He was a member of the Los Angeles County Medical Society, California and American Medical Associations, and the Los Angeles County Heart Association. He became a Fellow of the American College of Physicians in 1932.

Dr. Comstock was highly respected by the members of the medical profession and will be greatly missed by those who knew him.

Leland P. Hawkins, M.D., F.A.C.P.,
Governor for Southern California

DR. CHARLES V. CRANE

Charles Vernon Crane, M.D., F.A.C.P., of Grand Rapids, Mich., died October 10, 1948, of coronary thrombosis at the age of 66. He was a graduate of the Uni-

versity of Michigan Medical School in 1904, and had practiced in Grand Rapids for more than 25 years. He was one of Grand Rapids' leading internists and enjoyed the confidence of his patients and colleagues. A conscientious physician, he was interested in medical problems but always concerned about his patients' welfare. He leaves a host of loyal friends and associates.

Following his graduation from medical school, Dr. Crane interned in the U. S. Marine Hospital, Detroit, in 1904–1905. He practiced and held appointments from 1906 to 1916 in Tawas and Bay Cities. Entering the Medical Reserve Corps of the U. S. Army in 1916 as lieutenant, Dr. Crane served until 1919, when he was discharged as a lieutenant colonel. A diplomate of the American Board of Internal Medicine, Dr. Crane held appointments to the medical staffs of the Blodgett Memorial, Butterworth and St. Mary's Hospitals, and was consultant to the Clark Memorial and Isabella Homes.

Dr. Crane was elected to fellowship in the American College of Physicians in 1936. He was also a member or fellow of the Kent County and Michigan State Medical Societies, the American Medical, American Heart and American Diabetes Associations, and the Inter-State Post Graduate Medical Association of North America.

A. J. BAKER, M.D., F.A.C.P.

DR. OTHO AUGUST FIEDLER

Dr. Otho A. Fiedler of Sheboygan, Wis., a Fellow of the American College of Physicians since 1929, died June 22, 1948. Born at Stockbridge, Wis., March 9, 1873, Dr. Fiedler attended Marquette University School of Medicine and did postgraduate work at the University of Vienna. From 1902 to 1906, he served as Professor of Chemistry, and from 1912 to 1914, as Professor of Medicine at Marquette. He served in the Army Medical Reserve Corps in World War I and subsequently became Chief of Medical Service of the Sheboygan Clinic and St. Nicholas Hospital as well as Preceptor in the University of Wisconsin Medical School. A diplomate of the American Board of Internal Medicine, Dr. Fiedler was a past president of the Wisconsin State Board of Health, the Sheboygan County Medical Society, and the State Medical Society of Wisconsin; also a fellow of the American Medical Association.

DR. JAMES KING HALL

Dr. James King Hall, an organizer of Westbrook Sanatorium, Inc., Richmond, Va., and its president since 1911, died September 10, 1948. Born in North Carolina on September 28, 1875, Dr. Hall received the M.D. degree from Jefferson Medical College of Philadelphia in 1904, and the A.B. and LL.D. degrees from the University of North Carolina in 1901 and 1935, respectively. He was a diplomate of the American Board of Psychiatry and Neurology.

Dr. Hall was an associate editor of Southern Medicine and Surgery and of Diseases of the Nervous System. He was a former president of the American and Southern Psychiatric Associations, Association of Private Psychiatric Hospitals, Tri-State Medical Association of Virginia and the Carolinas, and the Richmond Academy of Medicine; a vice-president of the Medical Society of Virginia; and a member of many other professional organizations. A member of the old American Congress on Internal Medicine, Dr. Hall became an Associate of the American College of Physicians in 1923.

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